FIXED DRUG ERUPTION – AN ANALYSIS

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CERTIFICATE

Certified that this dissertation entitled ***"FIXED DRUG ERUPTION – AN ANALYSIS"*** is a bonafide work done by **Dr. NARMADHA DEVI.T.G,** Post Graduate Student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 600 003, during the academic year 2008 – 2011. This work has not previously formed the basis for the award of any degree.

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INTRODUCTION

World Health Organisation has defined a drug as "a substance or product that is used or intended to be used to modify or explore physiological system or pathological state of the recipient"[1].

Adverse drug reaction is defined by WHO as "a response to a drug that is noxious, unintended and undesired and occurs at doses used in man for modification of physiological function[2"]. ADRs affect upto 7% of the general population and constitute upto 8% of hospital admissions[3].

Cutaneous ADRs are among the more commonly observed adverse reactions to medications. Among the various morphological drug reaction patterns encountered, Fixed Drug Reactions account for upto one third of cases. According to many Indian studies, Fixed drug eruption is the most common cutaneous adverse drug reaction pattern, constituting 25-40% of cases[12,13]. In the western world, it is next only to maculopapular rash as the common cause of CADR[14,15,16]. Several studies analysing the epidemiological, pathophysiological, pharmacological and clinical aspects of FDE are available in literature. Though clinically less severe, FDE causes cosmetic embarrassment in many patients.

REVIEW OF LITERATURE

Adverse Drug Reactions are categorised into predictable (Type A) and unpredictable (Type B) reactions.

Predictable reactions are usually dose dependent, related to the known pharmacological actions of the drug and occur in otherwise healthy subjects. They account for 80% of the drug reactions. Unpredictable reactions are dose independent, unrelated to the pharmacological actions of the drug and occur only in susceptible subjects[2,4].

TYPE A – PREDICTABLE REACTIONS	TYPE B – UNPREDICTABLE REACTIONS
NONIMMUNOLOGICAL REACTIONS : - **OVERDOSAGE** - **SIDE EFFECTS** - **FACULTATIVE EFFECTS** - **DELAYED TOXICITY** - **DRUG REACTIONS** - **METABOLIC ALTERATIONS** - **EXACERBATION OF DISEASE** - **DRUG INDUCED CHROMOSOMAL DAMAGE** - **TERATOGENICITY**	➢ **NONIMMUNOLOGICAL REACTIONS :** - **DRUG INTOLERANCE** - **DRUG IDIOSYNCRASY** ➢ **IMMUNOLOGICAL : DRUG ALLERGY** (GELL AND COOMBS SYSTEM OF HYPERSENSITIVTY REACTIONS) • **TYPE I** - IMMEDIATE REACTIONS, MEDIATED BY IgE ANTIBODIES(Abs) • **TYPE II** - CYTOTOXIC REACTIONS, MEDIATED BY DRUG SPECIFIC Abs. • **TYPE III** - IMMUNE COMPLEX MEDIATED REACTIONS • **TYPE IV** - DELAYED TYPE HYPERSENSITIVITY REACTIONS

Type IV reactions can be subdivided into 4 Categories[5] involving activation and recruitment of

- Monocytes (Type IVa)
- Eosinophils (Type IVb)
- CD4+/CD8+ cells (Type IVc)
- Neutrophils (Type IVd)

There is also a recently proposed addition to the drug hypersensitivity reactions, where a drug noncovalently binds to a TCR without prior sensitisation, analogous to the concept of superantigens[6].

Numerous cutaneous eruptions have been attributed to drug induced allergic reactions which include

Type I reactions	:	Urticaria , Angioedema, Anaphylaxis
Type II reactions	:	Sedormid purpura, Thrombocytopenic purpura
Type III reactions	:	Serum sickness, Vasculitis, Arthus reaction, Rarely urticaria and anaphylaxis
Type IV Reactions	:	Exanthems, Fixed drug eruptions, Erythema multiforme, Steven Johnson Syndrome, Toxic Epidermal Necrolysis.

FIXED DRUG ERUPTION :

Fixed drug eruption represents an interesting cutaneous adverse drug reaction characterised by solitary or multiple, well circumscribed,

erythematous or dusky red patches, that may evolve into edematous plaques or bullae, with pruritus or burning sensation and characteristically recurs at the same site or sites, each time the drug is administered .With each exposure , the number of involved sites may increase and the lesions usually resolve with post inflammatory hyper pigmentation[7].

HISTORY :

In 1889, Bourns described a series of sharply demarcated hyperpigmented lesions on the lips and tongue of a patient who had recently ingested 20 g of antipyrine[8]. A few years later , Brocq coined the term 'eruption erythemato-pigmentee fixe' from which the term Fixed Drug Eruption is derived[9].

EPIDEMIOLOGY :

The incidence of FDE varies form 2.5% to 22%[10,11]. All ages are vulnerable. FDE has been reported in infancy[121] as well as in individuals as old as 87 yrs[40]. Most cases are in the age group of 20-40 years.

According to a study conducted in Pakistan, the mean age at presentation was 30.4 yrs in males and 31.3 years in females[40,72]. According to few recent studies, the ratio of male to female affected was almost equal. In earlier studies a male preponderance was noted[10,11].

Mode of exposure :

Ingestion – commonest[19]

Intravenous

Sublingual

Intradermal

Per-rectal

Inhalants[18]

Sexual transmission[20]

PATHOMECHANISM :

1. Genetic predisposition :

Familial cases of FDE have been reported across the world[21]. Recent reports indicated a significant association between FDE and HLA-class I antigens . A few associations are given below

Fepraxone - HLA B22

Cotrimoxazole - HLA – A30 B13 CW6

Naproxen - HLA A1 & B51[21,22]

2. Immunology :

Fixed drug eruption is a delayed cytotoxic T-cell mediated hypersensitivity reaction . It is thought to result mainly from autoimmune destruction of epidermal keratinocytes by T-cells, triggered by the offending drug[23].

Immunohistochemical characterisation of FDE lesions reveals the existence of significant numbers of CD8+Tcells in the basal or suprabasal location over a prolonged period of time even after clinical resolution[23,24]. These findings have led to hypothesize that these epidermal T-cells residing in FDE lesions, upon activation by a relevant antigen, could be involved in the disease process and may play a role in preserving the memory function of FDE. The intraepidermal CD8+ memory T cells established in resting lesional skin of FDE, on activation, produce large amounts of IFN. They transiently acquire a Natural killer cell like phenotype and express cytotoxic granules. They have high levels of perforins and are capable of producing IFN and TNFα[26,29]. According to one study, intraepidermal CD8+Tcells in FDE lesions use a very limited T-cell repertoire consisting of the Vα and Vβ gene families, when compared to the peripheral blood lymphocytes by quantitative PCR analysis[27]. This indicates that following reexposure to the causative drug, there is some expansion or preferential migration of epidermal T-cells that recognize a restricted set of antigens expressed within the epidermis.

FACTORS CONTRIBUTING TO PERSISTENCE:

The cytokines released by the CD8+ T-cells trigger the increased production of IL-15 by lesional keratinocytes, which in turn is a ligand for IL-2Rβ chain expressed by CD8+ T-cells[26.28]. There is also increased

expression of ICAM1 by lesional keratinocytes[24]. These two factors contribute to the survival of CD8+ T-cells within the lesional skin and result in repeated occurrence of FDE lesion at the same site.

MECHANISM OF RESOLUTION OF ACUTE EPISODES:

There is accumulating evidence that the CD4+ regulatory T cells play a role in the control of immune pathology. A significant number of CD25+,CD4+ reg T cells are recruited to the lesional skin 24 hours after challenge with the offending drug. The increased expression of IL-10 by these reg T-cells might suppress the effector memory function of CD8+T-cells in active FDE lesions bringing about clinical resolution[30,31].

HISTOPATHOLOGY :

Established lesions show a lichenoid reaction pattern. The histological changes resemble those of EMF and TEN. The inflammatory infltrate tends to obscure the dermoepidermal interface as in EMF. The infiltrates extend into mid and upper epidermis, producing death of keratinocytes above the basal layer.

Scattered necrotic keratinocytes with eosinophilic cytoplasm and pyknotic nuclei (referred to as Civatte bodies) are frequently seen in the epidermis and represent apoptosis. The frequent hydropic degeneration of basal cell layer leads to pigment incontinence, which is characterised by

the presence of melanin within macrophages in the upper dermis[32]. The degenerated keratinocytes show less shrinkage than in lichen planus[33]. In severe lesion ,a subepidermal cleft or bulla may form[32].

Fixed drug eruptions cannot be confidently distinguished from EMF and TEN. However the deeper extension of the infiltrate, the presence of few neutrophils and more prominent melanin incontinence, differentiate FDE from EMF[32].

Based on one study, it appears that a very early lesion may show epidermal spongiosis, dermal edema and neutrophil microabcess and numerous eosinophils in the demis. These features usually disappear after several days, although some eosinophils persist[34].

In the eczematous variant, spongiotic changes may be seen. Vasculitis is another pattern encountered[35]. In the nonpigmenting variant, these is mild perivascular and interstitial mixed inflammatory infiltrate in the dermis[36].

ELECTRON MICROSCOPY:

There is prominent clumping of tonofilaments in the cytoplasm with bright eosinophilic cytoplasm especially in the basal and supra basal layers. The accumulation of tonofilaments represents a response by keratinocytes to sublethal injury (or) some other stimulus[37].

The pigmentary incontinence develops when

a) macrophages invade the epidermis and phagocytize the necrotic keratinocytes together with their melanosomes

b) the necrotic macrophages return to dermis where they digest all the cellular remnants except for melanosomes[38].

The intraepidermal lymphocytes are largely CD8+ T cells, whereas the dermal perivascular and interstitial lymphocytes are predominantly CD4+ cells.

CLINICAL FEATURES :

The initial episode usually occurs few weeks after the intake of drug. The degree of sensitisation of an individual to a particular drug determines the first development of FDE. Once sensitisation occurs, the subsequent episodes develop within 30 minutes to 8 hrs[4,39].

Fixed drug eruptions classically manifest as sharply circumscribed round to oval patches, with violaceous or dusky erythema, which heal with hyperpigmentation in 6-10 days[39].The hyperpigmentation may persist for months to years . Cross reaction may occur with structurally similar drugs. The acute episode may be asymptomatic or associated with local symptoms like itching, burning or pain. Sometimes generalised itching may occur. Constitutional symptoms like fever, myalgia, arthralgia, nausea and vomiting have been described. Other symptoms

like abdominal cramps , anorexia , dysuria , disorientation and confusion may also occur[40]. Rarely FDE can manifest as pruritus ani or pruritus vulvae.

Koebnerisation was demonstrated in one study[41].Dermographism has been demonstrated over FDE lesions[43]. The lesions of FDE may increase in number and size with each subsequent episode, resulting in progressively bigger patches .The union of lesions may produce a polycyclic or band like pattern .Sometimes pruritus and burning may be the only manifestation of reactivation in a old patch[40].

SITE OF INVOLVEMENT :

The classical FDE mainly involves the limbs , hands, feet[42,46] and Genitalia[44] .Oral cavity[45] ,lips[46], perioral, periorbital, perianal areas[40] and conjunctivae[31] may also be involved.The lesions may be localised or generalised. These have also been reports of bilateral symmetrical distribution of lesions[18].

DRUGS IMPLICATED IN FDE :

Antibacterials

Ampicillin, amoxicillin[53,54]

Ceftriaxone[56]

Clindamycin[40]

Dapsone[62]

Nitroimidazoles[61]

Penicillins[53]

Rifampicin[118]

Sulphonamides (Cotrimoxazole)[51,52]

Fluoroquinolones[58,59]

Erythromycin, clarithromycin[60]

Tetracyclines[57]

Others - Arsenicals and Mercurials[42]

Antivirals

Acyclovir[63]

Foscarnet[64]

Antifungals

Clioquinol[71]

Griseofulvin[67]

Ketoconazole[66]

Fluconazole[68]

Itraconazole[70]

Nystatin

Terbinafine[69]

Antimalarials[72]

Sulfadoxine and pyrimethamine

Antiparasitic

Albendazole[40]

Levamisole[73]

Pyrantel palmoate[40]

Anti-inflammatory drugs

Aspirin[74]

Acetaminophen[75]

Celecoxib[76]

Oxyphenbutazone[45]

Diclofenac sodium[40]

Ibuprofen[77]

Indomethacin[40]

Mefenamic acid[40]

Naproxen[78]

Nimesulide[79]

Oxyphenbutazone

Piroxicam[49]

Antihistamine

Cetrizine[80]

Cyclizine[83]

Dimenhydrinate[85]

Diphenhydramine[82]

Hydroxyzine[84]

Levocetrizine

Loratidine[81]

Anticonvulsants

Carbamazepine[87]

Lamotrigine[88]

Phenytoin[87]

Sodium valproate[87]

Anti hypertensives

ACE inhibitors[89]

β blockers – Atenolol[89]

Calcium channel blockers[89]

Anticancer drugs

Docitaxel[90]

Paclitaxel[90]

Antipsycotic drugs – Barbiturates, Benzodiazepines[89]

Opioids alkaloids[91]

Miscellaneous

Allopurinol[40]
Anthralin
Belladonna[40]
Butazolidine[72]
Chloral hydrate
Chlormezanone[40]
Clopidogrel[96]
Multivitamins[103]
Omeprazole[89]
Ondansetron[146]
Quinine[102]
Papaverine[104]
Phenolphthalein[105]
Phenylpropanolamine[106]

Colchicine[90]
Cyproterone acetate[94]
Dipyrone[46]
Food substitutes & flavours[94]
Finasteride
Flecainide[95]
Infuenza vaccine[97]
Interferon[98]
Iopamide[99]
Lactose in botulinum toxin[100]
Methaqualone[101]
Metamizole[40]
Mouth wash – Chlorhexidine[102]
Pseudoephedrine[106]
Sorafenib[107]
Sodium fluorescein[89]
Sulfasalazine / sulfaguanide[89]
Sympatholytics[89]
Thiacetazone[50]
Ticlopidine[108]
Tonic water- quinine[109]
Tranexamic acid[110]

In addition fixed food eruption have also been described to tinned Asparagus, cashew nuts, lentils and strawberries[111,112].

DRUG SPECIFIC SITES OF INVOLVEMENT :

FDE on lips :

Certain drugs like naproxen and oxicams are the main inducers of FDE on lips. Others drugs reported include cotrimoxazole, ciprofloxacin, erythromycin and prochlorperazine[49,50].

Oral FDE :

Oral FDE can occur due to drugs like tetracyclines, oxyphenbutazone and Cotrimoxazole[45].

Genital FDE :

Isolated genital FDE can occur with tetracylines, cotrimoxazole and ampicillin[44]. There are reports of erosive vulvitis occurring following paracetamol[113].

Other sites :

Dipyrone, a pyrazolone derivative & Nonsteroidal Antiinflammaory Drug(NSAID) is reported to cause FDE on trunk & extremities. Dipyrone, aspirin and parcetamol spare lips, genitalia and trunk[50].

Other rare reports :

Rare reports of familial cases, nonpigmenting FDE, linear FDE, wandering FDE and solitary plaques over cheeks have been ascribed to cotrimoxazole[48]. A rare report of naproxen induced FDE with peculiar unilateral breast involvement is available in literature[115].Constitutional symptoms are commonly observed with levamisole and thiacetazone[50].

OTHER MORPHOLOGICAL PATTERNS :

1) Bullous FDE:

Bullous FDE usually produces multifocal lesions characterised by multiple, large, sharply defined deeply red patches and blisters, displaying a bilaterally symmetrical distribution, with a predilection for

extremities, genitalia and intertriginous sites[116-118]. It occurs abruptly and continues to increase in size and number even after cessation of the offending drug. Mucosal sites are usually spared and constitutional symptoms are mild[121,122]. Recovery is complete without sequelae. There are reports of bullous FDEs occuring with drugs like cetrizine[123], flecainide[95], fluconazole[68], fluoroquinolones[58], metronidazole[120], naproxen[124], paracetamol[75], paclitaxel[90], rifampicin[118], influenza vaccination[97] etc.

Nonpigmenting bullous FDE has been reported with pseudoephedrine[106]. Widespread bullous FDE may mimic SJS & TEN clinically. It is important to distinguish bullous FDE from the other two CADRs, as it carries a good prognosis. A histopathological examination may help in differentiation between FDE, SJS and TEN. Epidermal changes cannot be differentiated and vary from a few scattered necrotic keratinocytes to full thickness epidermal necrosis. Presence of intraepidermal vesiculation with ballooning degeneration and keratinocyte necrosis makes the diagnosis of FDE more likely. Close examination of the dermis is helpful for differentiation. In SJS and TEN, the infiltrate is lymphohistiocytic and tends to be located solely around superficial plexus. In FDE, in addition, a mixed inflammatory infiltrate containing neutrophils and eosinophils in addition is noted around superficial and deep plexuses[125-127].

Non pigmenting FDE (NPFDE) :

The concept of NPFDE was first proposed by Abramovitz and Noun in 1937[128]. This variant has been associated with drugs like pseudoephedrine[106], phenylpropanolamine[106], tetrahydrozoline[129], piroxicam[130] ,radioopaque contrast medium iothalmate[131], ,diflunisal[132], indomethacin, arsphenamine, thiopental[133] paracetamol[134],intraarticular triamcinolone acetonide[135] and eperisone hydrochloride[136].

Pseudoephedrine has been the commonest cause of NPFDE and forms an important constituent of many Japanese and Chinese herbal medicines (Ephedra hebra especially)[65].

NPFDE poses a clinical challenge, as the replicate nature of eruption exists without the physical clues that is recogonisable with the pigmenting forms of FDE. NPFDE has been characterised by multiple symmetrically distributed lesions

The site of hypersensitivity response is considered to be dermal according to a few studies. In a study done to determine the factors responsible for the lack of pigmentation before challenge, the NPFDE lesions are characterised by large number of CD8+ intraepidermal T-cells and paucity of melanocytes, when compared with pigmented FDE lesion.

Very high levels of serum IL-10 were noted after clinical challenge. NPFDE with epidermal involvement may be an abortive form of SJS/TEN in which progression to TEN can be prevented by IL- 10[137].

3) Erythema multiforme like FDE[127]

4) Linear FDE – Trimethoprim, Cephazoline.

The linearity may be related to the distribution of the dermatoses, Blaschko's lines, skin tension lines and anatomical structures[138].

5) Wandering FDE[139]

6) Morilbilliform/Scarlatiniform FDE

7) SJS / TEN like FDE

8) Urticaria like FDE[41]

9) LP like FDE

10) Paronychia

12) Chelitis

13) Psoriasisform FDE

14) Housewife's eczema like FDE

15) Melasma like FDE

16) DLE like FDE

17) Erythema annulare centrifugum like FDE

18) Pemphigus vulgaris like FDE

19) Chilblain like FDE

20) PR like FDE

21) Vulval /perianal melanosis /periorbital[40]

Complication and prognosis :

Local - Secondary infection

- Residual hyperpigmentation

Prognosis is good. No deaths have been reported so far.

CROSS REACTIVITY :

Cross reaction can occur to drugs with similar structures. The cross reactivity of drugs within a pharmacological group is not an all or none phenomenon. Cross reactivity is commonly observed among the following group of drugs.

- Among paraamino group of compounds in sulphonamides induced FDE[140]
- Among nitroimidazole group of drugs[61]
- Among azoles – esp fluconazole & itraconazole[141]
- Among fluoroquinolones[142]
- Among tetracycline group of drugs[143]

Knowledge about cross reactivity may be quite useful for selecting alternative drugs.

POLYSENSITIVITY :

It is the occurrence of FDE as a reaction to multiple drugs with chemically unrelated structures in the same patients. The lesions may occur on identical or separate sites. The incidence is 0.2-0.8%[148].

Reported cases of polysensitivity :

- Metamizole and saridon
- Metamizole and penicillin G
- Oxyphenbutaxone and Phenobarbital
- Metamizole and tetracycline[143]
- Ampicillin,ibuprofen and acetyl salicyclic acid[144]
- Phenytoin,sodium valproate and carbamazepine[145]
- Paracetamol and tropisetron – ondansetron[146]
- Doxycycline and metronidazole[147]
- Cotrimoxazole and tenoxicam[148]

Shiohara and Kokaji claimed that drugs and foods containing nonspecific mastcell degranulators such as acetyl salicylic acid and

bacterial toxins or physical stimuli such as friction can induce rapid local release of cytokines from mastcells like TNFα. This provides a localised initiating stimulus for residing epidermal T-cells, thus producing reactivation of FDE lesions[149].

DIAGNOSIS OF FDE :-

An exact history and description of clinical manifestation is mandatory. History taking should include details of all drugs taken by the patient before the reaction. It is also important to know the dates the treatment was begun and stopped ,the mode of drug administration, the prescribed dosage and the disease for which it was prescribed. Many algorithms are available to establish the causality of a particular drug in drug eruptions like those devised by Jones[150], Naranjo[151], Kramer et al[152] and WHO.

WHO UMC Criteria for causality assessment :

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs

- ❖ Response to withdrawal plausible (pharmacologically, pathologically)
- ❖ Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a known pharmacological phenomenon).
- ❖ Rechallenge satisfactory, if necessary

Probable /Likely

- ❖ Event or laboratory test abnormality, with reasonable time relationship to drug intake
- ❖ Unlikely to be attributed to disease or other drugs
- ❖ Response to withdrawal clinically reasonable
- ❖ Rechallenge not required

Possible

- ❖ Event or laboratory test abnormality, with reasonable time relationship to drug intake
- ❖ Could also be explained by disease or other drugs
- ❖ Information on drug withdrawal may be lacking or unclear

Unlikely

- ❖ Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- ❖ Disease or other drugs provide plausible explanations

Conditional /Unclassified

- ❖ Event or laboratory test abnormality
- ❖ More data for proper assessment needed, or
- ❖ Additional data under examination

Unassessable/Unclassifiable

- ❖ Report suggesting an adverse reaction
- ❖ Cannot be judged because information is insufficient or contradictory
- ❖ Data cannot be supplemented or verified[153]

DRUG TESTS AVAILABLE TO DETERMINE THE CAUSE OF FDE:

IN VIVO TESTS	INVITRO TESTS
• Drug skin tests ➢ Patch test / Repeat application test ➢ Skin prick test ➢ Intradermal skin test[154] • Challenge test/provocation test[157]	➢ Lymphocyte transformation test ➢ CD69 upregulation test ➢ Measurement of drug induced cytokine production from peripheral blood mononuclear cells[158]

The diagnosis of drug hypersensitivity reaction continues to be a challenge, as the optimal skin test concentrations for several drugs are yet to be determined. The few in vitro tests that are available are not validated[158].

A negative topical provocation test result does not exclude the responsibility of a drug in the causation of FDE . However these tests have a high degree of specificity[155,158]. Therefore in case of doubt, the potential drug should be withdrawn from further pharmacotherapy, or alternatively, a drug provocation test has to prove the clinical relevance and results. But the ethical issues related to drug provocation tests and the risk benefit ratio should be taken into account before performing the tests[156].

Patch test :-

Drug patch testing has been found to elicit positive response in about 50% of cases with FDE, when there is a high drug imputability[158]. In populations with low imputability for the tested drug, patch tests were positive only in 10% of cases[159].

Pathogenesis of local reaction in patch testing :-

This test relies on the penetration of the drug from the patch into the epidermis where the hapten – either the parent drug or the reactive metabolite formed by the drug metabolising enzymes in the skin, conjugate with host proteins. Conjugates are recognised by MHC expressing antigen presenting cells which process and present them to effector cells of immune system. This triggers peptide specific CD8+T cells to get activated and release proinflammatory cytokines and chemokines causing a local response[160] .

Apart from the time course , the reactions are different from the patch test in allergic contact dermatitis both in clinical aspects and their pathology. For instance, in some studies, isolated symptoms like pruritus, eventually associated with faint erythema are occasionally considered as a positive reaction[162] .

A working party of European Society of Contact Dermatitis has proposed the guidelines for performing skin testing in CADR in an attempt to standardize these procedures[155].

GUIDELINES :

General procedures:

Patch tests are usually performed with Finn chamber fixed on Scanpor tape. Ideally the test should be performed both on normal skin on the back and on the residual pigmented site of FDE.

After informed consent, drug skin tests should be performed 6 weeks to 6 months after complete healing of the skin lesions. The testing is not usually recommended after 8 months of healing of lesion, as possibility of obtaining negative results is very high. It is preferable not to test during pregnancy. Overfilling or under filling can lead to false positive or false negative results respectively.

CONCENTRATION AND VEHICLES :

Patch testing with commercialised drug :

The drug possibly responsible for FDE can be tested with the commercialised drug formulation used by the patient. Pills should have their coating removed and then ground to a very fine powder. Using the powder, a 30% concentration of the drug is prepared either with

petrolatum, DMSO, distilled water or 95% alcohol as vehicle. Each preparation is made for only one patient and can be kept for only one day. Whenever possible the drug coating, preservatives, colouring agents and excipients should also be tested undiluted or diluted at 10% in petrolatum. The gel jacket portion of capsule should be moistened and tested as is. The highest non irritating concentration is preferred to minimise false negative results[155].

Patch testing with pure substance:-

Whenever possible, the pure drug obtained from the manufacturer should be tested, diluted at 10% in petrolatum and if possible also at 10% in aqua or alcohol Recently, standardised material with pure molecules, diluted in petrolatum has been commercialised for drug patch tests for some drugs(by Chemotechnique laboratory, Sweden)[163].

Drug or Drug Class	Concentrations Used and Controls (when available)	Relapse of the CADR Caused by Drug Patch Tests
Acetylsalicylic acid	C*:10% in petrolatum	—
Acyclovir	Commercialized form - as is, 20%, 10% and 1% in pet[159] 10% in pet[164] C*: 10% in pet	—
Betalactam antibiotics[154.159] Amoxicillin[165] PenicillinG, potassium salt Cefotaxime Cephalexin Dicloxacillin sodium[154,166]	10% in pet C*: 10% in pet C*: 10% in pet 10% in pet 10% in pet 10% in pet	Immediate reactions in case of anaphylaxis
Captopril[154,167]	1% and 10% in pet[167]	—
Carbamazepine[155,168,169]	10% in pet C*: 1% in pet	[155]

Drug or Drug Class	Concentrations Used and Controls (when available)	Relapse of the CADR Caused by Drug Patch Tests
Celecoxib Frequent false positive reaction[170]	tested at 10% or 1%in pet	—
Chloroquine No true positive reaction	False positive reactions The threshold of specificity undetermined[171]	—
Chlorpheneramine[172]	20% in pet (commercialized form)	—
Clindamycin	C*: 10% in pet	—
Ciprofloxacin[173]	10% 1n pet	—
Clarithromycin	C*: 10% in pet	—
Codeine[174]	1% and 5% in pet	—
Colchicine[171] False positive results	10% in pet,(80% of negative controls - false-positive results)[171]	—
Corticosteroids[154,175]	If negative, to be diluted in ethylalcohol[154]	—
Cotrimoxazole[176]	10%, 20% or 50% in DMSO, frequently negative when diluted in pet[155] C*: 10% in pet	—
Cyclines[177] Doxycycline Minocycline	0.1% and 1% in a DRESS C*: 10% in pet 10% in pet	—
Desloratadine[178]	Diluted at 10% in pet in 8/10 volunteers, specific when tested diluted at 1% in pet[178]	—
Diclofenac[179]	1% in pet C*: 1% in pet	At 1% pet in an anaphylactic shock[158]
Erythromycin	C*: 10% in pet	—
Fluoroquinolones [154,59] Norfloxacin Ciprofloxacin	30% in pet or water (commercialized form) C*: 10% in pet 10% in pet	—
Hydantoin	C*: 10% in pet	
Hydroxyzine[154]	10% in pet C*: 1% in pet	[154]
Ibuprofen	C*: 10% in pet	—
Ketoprofen	C*: 1% in pet	—
Terbinafine[154]	As is[154]	—
Metamizole[180]	1% ,10% in petrolatum	
Metronidazole[154]		—
Nimesulide[79]	10% in pet (commercialized form)	—
Omeprazole[171] No true positive reaction	30% in pet or water (commercialized form)	—
Oxicams[130]	1% in pet or 10% in pet C*: piroxicam 1% in pet	—
Paracetamol	C*: 10% in pet	–
Pseudoephedrine,[181]	Tested at 1% in pet to avoid any relapse of the CADR	

Pet – Petrolatum **C* - Chemotechnique lab**

Advice to patient:-

Patient should be adviced to keep the patch dry, avoid vigorous activities and sunlight exposure.

Reading:-

Patch test reactions need to be read at 20 min, day 2 and day 4 (if not possible on day3). Whenever possible if the patch tests are negative on day 4, a reading a should be performed on day 7. As drug patch tests can elicit immediate positive reactions especially with β-lactam drugs, a reading at 20 minutes is made. Results of patch testing should be reported according to the International Contact Dermatitis Research group (ICDRG) criteria[182].

ICDRG CRITERIA :

Clinical picture	Score	Conclusion
Faint erythema only	? or +ve	
Erythema, infiltration possibly discrete papules	+	
Erthema, infiltration, papules, vesicles	++	
Intense erythema, infiltration, coalescing vesicles	+++	
	- ve	Negative
	IR	Irritant Reaction
	NT	Not Tested

As already mentioned, isolated symptoms like pruritus, eventually associated with faint erythema can be considered as a positive reaction. With patch tests , cross reactions have been demonstrated. The reactivity pattern differs from one patient to another and no general rule of cross reactivity can be given[163].

Drug free intervals demanded for drugs decreasing reactivity of patch tests :

It is preferable to discontinue systemic steroids or immunosuppressive therapy at least 1 month before patch testing[183] .

DRUG FREE INTERVALS :

Medication	Routes	Drug free interval
H1 antihistamines	Oral, IV	5 days
B – adrenergic drugs	Oral, IV	5 days
Glucocorticosteroids Long term Short term,high dose Short term,<50mg prednisolone	 Oral, IV Oral, IV Oral, IV	 3 wks 1 wk 3 days
Topical steroids		2 wks

FALSE positive results :

- ✓ Allergy to vehicle itself – very rare with petrolatum
- ✓ Allergy to some other component of commercialised drug
- ✓ Over filling of Finn chamber

FALSE negative results :

- ✓ Inadequate concentration of the drug
- ✓ Drug not uniformly dispersed in vehicle - poor absorption
- ✓ Metabolite rather than the drug is the sensitising antigen
- ✓ Coadministration of immunosuppressive drugs
- ✓ Exposure to sunlight
- ✓ Underfilling of Finn chamber

Other Pit falls :

- ❖ Drug patch tests can reactivate FDE in few cases
- ❖ Patch tests have high positive predictive value and low negative predictive value[163].

SKIN PRICK TEST (SPT)

They are of unknown significance in diagnosing fixed drug eruption. They are done on the volar aspect of the forearm with the commercialised form of the drug .Whenever possible both the pure drug and excipients should be tested. The concentration is the same as that for patch test. A SPT is done by pricking the skin percutaneously with a prick needle through the drug solution. Reaction are considered positive when a wheal with a diameter >3mm than that of negative control appear.If

control is positive, a wheal of diameter 3 mm more than control is considered positive. Reading is usually taken at 20 min and one day later[155].

INTRADERMAL SKIN TESTS:

When SPT gives a negative result, intradermal test can be done.

Guidelines :

- Dilutions are prepared under laminar flow no longer than 2 hrs preceeding administration.
- Intense monitoring of patients is a must as IDT can precipitate CADRs.
- Sterile solutions of the suspected drug diluted sequentially (10-4, 10-3, 10-2, 10-1) in phenolated saline or in 0.9% saline is used.
- The tests are performed on the extensor surface of the arm , with a 0.04ml that produces a wheal of 4-6 mm in diameter.
- Tests are initially read after 30 minutes with each serial dilution. A wheal of > 10 mm diameter is considered positive.
- Intradermal test result readings are taken at 30 min, 6 hrs & 1 day .
- When the results are negative, a delayed reading at 1 wk should be taken.

Among these skin tests available drug patch testing is found to be more useful. The significance of SPT & IDT in FDE is unknown[155].

DRUG PROVOCATION TEST :

Provocation tests are regarded as gold standard to establish or exclude the presence of hypersentivity to a drug. Provocation testing is potentially harmful and should be considered only after balancing the risk benefit ratio in a patient.

It is defined as a controlled administration of a drug under medical surveillance to diagnose drug hypersensitivity

Procedure :

General guidelines for DPT have been proposed by the European network for Drug Allergy and the European Academy of Allergology and Clinical Immunology interest group on hypersensitivity :

- DPTs should be performed 4 wks after drug hypersensitivity or after at least five drug elimination cycles have passed since the ADR episode.
- The drug should be administered by the same route and in the same form that it was originally taken.
- Escalating doses should be used.

- ❖ Comedication that could affect the drug pharmacokinetic profile should be eliminated.
- ❖ The patient should be in good health with no comorbidity risks.
- ❖ Rechallenge should take place in a controlled environment with resuscitation facilities.
- ❖ Good documentation following controlled protocols and assessment systems should be used to document responses.
- ❖ Contraindications include pregnancy, significant comorbidity, increased risk caused by life-threatening reactions such as the bullousreactions, erythroderma, DHS, anaphylaxis, systemic vasculitis, and drug induced autoimmune disease.
- ❖ No alternate tests are available to aid diagnosis.

As a rule commercialised preparations are used and Compounds should be tested separately in sequence in case of multiple drug intake. The time interval between doses should be atleast 30 minutes. Depending on the drug and patient's response threshold, a DPT may be concluded with in a few hrs, days or occasionally weeks.

DPT may also be performed to find an alternative drug in which case, the maximum single therapeutic dose should be achieved.

Test Results :

A DPT may be considered + ve if it reproduces the original symptoms or atleast objective ones[156]

MANAGEMENT :

- Withdrawal and avoidance of the offending drug :

  The physician should advise the patient regarding

  a. Drug(s) that may have caused the eruption and those to be avoided.

  b. Drug(s) that can be used

- Symptomatic treatment with antihistamines ,emollients

- Oral and topical steroids

- Topical triple drug combination – topical steroids, retinoids and hydroquinone for residual hyper pigmentation

- There are reports of successful desensitisation to allopurinol in patients with FDE to allopurinol[190].

AIM

- To find out the incidence, age and sex distribution of Fixed Drug Eruption among patients attending the Department of Dermatology, Government General Hospital, Chennai.
- To find out the proportion of FDE cases among various cutaneous adverse drug reactions.
- To find out the common offending drugs and study the drug specific clinical patterns and sites of involvement in the FDE cases.
- To study the different parameters of fixed drug reaction - Number of episodes in a patient and mean length of time from drug exposure to the development of FDE lesions during initial and subsequent episodes.
- To confirm the drugs responsible for causation through patch testing.
- To study the various histopathological characteristics of fixed drug eruptions.
- To ascertain the role of CD8+ T-cells in causation through Immunohistochemistry.

MATERIALS AND METHODS

STUDY PERIOD AND DESIGN :

A cross sectional study where in 76 patients who presented with Fixed drug eruption to the Department of Dermatology, Government General Hospital, Chennai from Aug 2008- Aug 2010 were analysed.

Patients with Fixed drug eruptions attending or referred to our department with definite history of drug intake prior to the onset of lesion were included in the study. The approval of the ethical committee was obtained before commencing the study.

CLINICAL PROFILE :

The history and clinical examination of selected subjects were recorded on a predesigned proforma. Preliminary informations like age, sex, occupation and addresses were noted down.

A detailed inquiry was made on the following aspects

- Nature of the drug (Allopathy /Others)
- Drug Details :
    - Name of the drug/ drugs
    - Single or multiple
    - Complaints for which they were prescribed

- Duration of lesions
- Number of episodes of FDE
- Time interval between drug exposure and occurrence of lesions
- Site of occurrence and Nature of lesions
- Increase in number and size of FDE lesions during subsequent episodes in recurrent cases
- Associated local and systemic symptoms
- Others
  - History of atopy
  - Family history of drug allergy
  - Sexual history

Each patient was subjected to a thorough general and systemic examination. Dermatological examination included the morphological pattern of drug eruption, site of lesions and number of lesions.

Haematological investigations included Complete blood count and absolute eosinophil count. Blood VDRL and HIV ELISA testing were done in all patients.

The causality of the suspected drug was established by using 'WHO-MHC causality assessment criteria'. Patch testing was done in all willing patients in an effort to identify the causative drug. The test was

done according to the guidelines proposed by the European society of contact dermatitis.

Drug patch testing was done 6 weeks after complete healing of lesions. The test was deferred in pregnant women and in patients with FDE lesions of more than 8 months duration. Prior to testing, patients were asked to abstain from potentially offending drugs, antihistamines, steroids and immunosuppressives. Topical corticosteroids were discontinued atleast 2 weeks prior to the test. Patients were asked to avoid sun exposure and vigorous activities.

The test was done on both the lesional skin and the unaffected skin on the back. In cases with mucosal FDE, patch testing was done on normal skin of the back. In patients with unknown drug history, patch testing was done with the common offending agents, based on the complaint for which the drug was prescribed.

A standard concentration of the incriminated drug was prepared by dispersing the commercialised drug form in petrolatum and applied using a Finn chamber on Scanpor tape. The readings were taken on day 2 and day 4, and graded based on ICDRG criteria[182]. As followed in few previous studies, isolated local symptoms like itching and burning sensation were also considered to be positive[162].

Biopsy was done in 33 patients after informed consent and the specimen was subjected to histopathological examination, after staining with Hematoxylin and Eosin.

Immunohistochemical analysis using antibodies to CD8 was done in 8 patients (4 with acute lesions and 4 with residual hyperpigmented patch). Intradermal and oral provocation tests were deferred, as it was not possible to get the approval of the ethical committee of our institution.

OBSERVATIONS

INCIDENCE :

The incidence of fixed drug eruptions among OPD patients was found to be 0.54%. FDE was the second common cutaneous adverse drug reaction pattern constituting 24.83% cases (76 out of 306). Maculopapular rash was the most common cutaneous adverse drug reaction pattern constituting 29.25% of cases.

AGE AND SEX DISTRIBUTION

The maximum number of cases were in the age group of 21-30 yrs constituting 46.1 %(n = 36). The youngest patient was 8 months old and the oldest patient was 75 years old. The male to female ratio was 1.23:1 (42:34). The mean age of male patients was 30.69 years (S.D ± 14.75) and that of females was 31.91 years (S.D ± 13.35).

AGE&SEX DISTRIBUTION (Fig. 1)

Age group		SEX		Total
		Male	Female	
≤ 10 yrs	No.of cases	2	1	3
	% within age group	66.7%	33.3%	100.0%
	% of Total	2.6%	1.3%	3.9%
11-20 yrs	No.of cases	3	3	6
	% within age group	50.0%	50.0%	100.0%
	% of Total	3.9%	3.9%	7.9%
21-30 yrs	No.of cases	20	15	35
	% within age group	57.1%	42.9%	100.0%
	% of Total	26.3%	19.7%	46.1%
31-40 yrs	No.of cases	8	7	15
	% within age group	53.3%	46.7%	100.0%
	% of Total	10.5%	9.2%	19.7%
41-50 yrs	No.of cases	4	4	8
	% within age group	50.0%	50.0%	100.0%
	% of Total	5.3%	5.3%	10.5%
51-60 yrs	No.of cases	3	3	6
	% within age group	50.0%	50.0%	100.0%
	% of Total	3.9%	3.9%	7.9%
> 60 Yrs	No.of cases	2	1	3
	% within age group	66.7%	33.3%	100.0%
	% of Total	2.6%	1.3%	3.9%
Total	No.of cases	42	34	76
	% within age group	55.3%	44.7%	100.0%
	% of Total	55.3%	44.7%	100.0%

P value - 0.667 (insignificant difference in sex incidence)

DURATION OF LESION:

DURATION OF FDE	NO : OF PATIENTS
< 1 WEEK	8 (10.52%)
1 - 4 WEEKS	4 (5.26%)
1 - 6 MONTHS	5(6.58%)
6 - 12 MONTHS	4(5.26%)
1 - 2 YEARS	38(50%)
2 - 4 YEARS	17(22.36%)

The duration of lesions varied between 2 days and 4 years. On an average the time period of an acute episode was 4.2 weeks. In patients with recurrent episodes, the disease was present for a duration of less than a year in 11.29 % of cases, for 1-2 years in 61.29% cases and for 2-4 years in 27.42%.

NUMBER OF EPISODES (Fig.2):

NO : OF EPISODES	NO : OF CASES	PERCENTAGE
1	14	18.4
2-5	51	67.1
5-10	11	14.5
TOTAL	76	100

14 patients (18.4%) had developed FDE for the first time.51 patients (67.1%) had 2-5 episodes and 11(14.5%) had suffered 6-10 episodes.

MEAN TIME INTERVAL :

EPISODE OF FDE	MEAN TIME INTERVAL
FIRST EPISODE	13.4 DAYS
SUBSEQUENT EPISODES	4.65 hrs

A statistically significant difference was observed with regards to the incubation period in the initial and subsequent episodes. The mean time interval between drug intake and occurrence of FDE was found to be 13.4 days (S.D ± 4.75 days) in the first episode. The minimum time interval noted was 7 days and the maximum time interval was 22 days. The mean time of onset of lesions in subsequent episodes was 4.65 hrs (S.D ± 2.89 hrs). The minimum time interval noted was 20 minutes and the maximum time interval was 36 hrs.

MORPHOLOGICAL PATTERN OF PRESENTATION:

MORPHOLOGICAL PATTERN	NO : OF CASES	PERCENT
CLASSICAL	62	81.57%
BULLOUS	14	18.42%
NONPIGMENTING (Bullous)	1	1.33%

The FDE lesions were mainly of the classical type in 65.8% (n = 62) of cases, with initial erythematous, edematous patches healing with residual hyperpigmentation. Bullous FDE was the presenting feature in 18.42% (n = 14). There was one (1.33%) interesting case of nonpigmenting FDE involving the palms.

DISTRIBUTION OF LESIONS:

PATTERN OF DISTRIBUTION	NO : OF CASES WITH PERCENTAGE
LOCALISED SOLITARY	12(15.79%)
LOCALISED MULIPLE	5(6.57%)
MULTIFOCAL	41(53.95%)
GENERALISED	4(5.26%)
TOTAL	76

The lesions were multifocal in 53.95% cases (n = 41), solitary in 15.79%cases (n = 12) and generalised in 5.3% cases (n = 4) .For the patients with solitary lesions, it was their first episode of FDE.

NUMBER OF LESIONS:

NO : OF LESIONS	NO : OF PATIENTS
1	12(15.79%)
2 – 5	28(36.84%)
6 – 10	23(30.26%)
11 – 30	9(11.84%)
> 30	4(5.3%)

12 patients (15.79%) had single lesion, 28 patients (36.84%) had 2-5 lesions, 23 patients (30.26%) had 6-10 lesions, 9 patients (11.84%) had 10-30 lesions and 4 patients (5.3%) had generalised involvement with more than 30 lesions. 55(85.94%) out of 62 patients with recurrent episodes showed increase in size and numbers of lesions during subsequent episodes.

SHAPE AND SIZE OF LESION:

The lesion were mostly circular seen in 84.21%patients (n = 64). 11.84% patients (n = 9) had presented with irregular hyperpigmented patches and 3.9% (n = 3), with large polycyclic lesions. The size of the lesions varied from 0.5 cm to 15 cms.

DRUGS INCRIMINATED IN CAUSATION (Fig.3):

There was a definite history of drug intake in all patients. All of them had developed FDE after intake of allopathy drugs. None of them gave history of intake of indigenous medicine prior to the onset of lesions. There was no family history of drug allergy in any of them. There was no personal or family history of atopy in any of them.

The exact drug details were known only in 63 patients (82.9%). 49 out of them (77.78%) gave history of single drug intake in the form of over the counter medications and 14 (22.22%) had history of intake of

multiple drugs. In the remaining 13 patients (17.11%), the drug details were not known.

The identification of the offending drug was confirmed by patch testing in 25 out of 64 willing patients (32.9%). It was negative in the remaining 39 patients. 6 patients (7.9%) were not willing for patch testing and 4 patients (7.9%) failed to report for follow up. Among the 39 patients with negative patchtest results, 7(17.94%) had mucosal FDE and 6 (15.38%) presented with unknown drug details.

NAME OF DRUG	FREQUENCY	PERCENT
CIPROFLOXACIN	11	14.5
COTRIMOXAZOLE	9	11.8
LEVOFLOXACIN	8	10.5
DICLOFENAC	7	9.2
PARACETAMOL	6	7.9
PHENYTOIN	5	6.6
DOXYCYCLINE	4	5.3
METRONIDAZOLE	4	5.3
NORFLOXACIN	2	2.6
BRUFEN	2	2.6
CARBAMAZEPINE	2	2.6
CHLOROQUINE	1	1.3
FLUCONAZOLE	1	1.3
NIMESULIDE	1	1.3
DETAILS UNKNOWN	13	17.1
TOTAL	76	100

Fluoroquinolones were the most common offending group of drugs. Ciprofloxacin topped the list, responsible in 11 cases (14.5%) followed by levofloxacin in 8 cases (10.5%). Cotrimoxazole induced FDE in 9 cases (11.8%), out of which 4 were children less than 14 years of age. The other antibacterials included doxycycline, metronidazole which accounted for 4 cases each (95.3%) and norfloxacin which was the offender in 2 cases (2.6%).

Nonsteroidal anti-inflammatory drugs were the second commonly incriminated group of drugs with diclofenac being the causative drug in 7 cases (9.2%), followed by paracetamol in 6 cases (7.9%).

Among the anticonvulsants, the main inducer was phenytoin involved in 5 cases (6.6%).

SITE OF INVOLVEMENT:

The most frequently involved site was extremities (n = 34; 44.73%), followed by the trunk (n = 26; 34.2%), face (n = 17; 22.4%) and mucosa (n = 14; 18.42 %). Others less frequent sites included palms and soles (n = 6, 7.9%), lips and perioral areas (n = 7, 9.2%).

SEX SPECIFIC SITE OF INVOLVEMENT (Fig.4):

SITE OF FDE	MALE	FEMALE	P - Value (Chi square)
EXTREMITIES	15(44.1%)	18(55.9%)	0.079
TRUNK	13(50%)	13(50%)	0.506
FACE	7(41.2%)	10(58.8%)	0.185
ORAL MUCOSA	6(75%)	2(25%)	0.092
GENITALIA	6(85.71%)	1(14.28%)	0.089
LIPS AND PERIORAL	2(28.6%)	5(71.4%)	0.136
PALMS AND SOLES	5(83.3%)	1(16.7%)	0.150

The collected data was statistically analysed using SPSS, version 15 for windows. There was also no statistically significant difference in the involvement of face, lips, trunk, extremities, mucosa and palms and soles between males and females. However, clinically oral and genital involvement were most frequently documented in males, with oral involvement seen in 75% (n = 6) of males and genital involvement in 85.71% (n = 6) of males. Lip and perioral involvement was more frequently encountered in females (71.4%). Males predominantly showed involvement of palms and soles (83.3%) when compared to females (16.7%).

DRUG SPECIFIC SITE OF INVOLVEMENT (Fig.5):

NAME OF THE DRUG	EXTREMITIES (n = 41)	TRUNK (n = 26)	FACE (n = 17)	ORAL MUCOSA (n = 8)	GENITALIA (n = 7)	LIPS & PERIORAL (n = 7)	PALMS & SOLES (n = 6)	OTHERS
CIPROFLOXACIN (11)	7 (63.63%)	4 (36.36%)	2 (18.18%)	1 (9.09%)	1(9.09%)	1(9.09%)	-	-
COTRIMOXAZOLE (9)	2 (22.22%)	3 (33.33%)	2 (22.22%)	2 (22.22%)	2 (22.22%)	2 (22.22%)	-	PERI OCULAR
LEVOFLOXACIN (8)	5 (62.5%)	2 (25%)	5(62.5%)	1 (12.5%)	1 (12.5%)	-	-	-
DICLOFENAC (7)	1 (14.28%)	4 (57.14%)	2 (28.57%)	2 (28.57%)	-	2 (28..57%)	1 (14.28%)	-
PARACETAMOL (6)	4 (66.67%)	-	-	-	-	-	4 (66.67%)	-
PHENYTOIN (5)	-	5(100%)	-	-	-	-	-	-
DOXYCYCLINE (4)	1 (25%)	-	1 (25%)	1 (25%)	1 (25%)	-	-	-
METRONIDAZOLE (4)	-	3 (75%)	2 (50%)	1 (25%)	-	-	1 (25%)	-
NORFLOXACIN (2)	-	-	2 (50%)	-	-	1 (50%)	-	-
BRUFEN (2)	2 (100%)	-	-	-	-	-	-	-
CARBAMAZEPINE (2)	1 (50%)	1 (50%)	-	-	-	-	-	-
FLUCONAZOLE (1)	1 (100%)	-	-	-	-	-	-	-
NIMESULIDE (1)	-	1 (100%)	-	-	-	-	-	-
CHLOROQUINE (1)	1 (100%)	-	-	-	-	-	-	-
DETAILS UNKNOWN(13)	9 (69.23%)	4 (30.77%)	1 (7.69%)	-	1 (7.69%)	1 (7.69%)	-	-

The data concerning the FDE sites and FDE inducer drugs was statistically analysed using SPSS, version 15 for windows to identify the relation of FDE sites to the drugs incriminated in causation. Statistical evaluation was done using chi- square tests and p values lower than 0.05 were considered significant. The results of the analysis showed no statistical association was found between FDE sites and FDE inducer drugs.

NAME OF THE DRUG	SITE	P – VALUE
CIPROFLOXACIN	EXTREMITIES	0.818
LEVOFLOXACIN	FACE	0.5
PARACETAMOL	PALMS & SOLES	0.667
PHENYTOIN	TRUNK (100%)	COMPARISON IMPOSSIBLE

Though statistically insignificant, certain clinically significant associations found in our study are as follows :

i. Ciprofloxacin more frequently induced lesion on extremities (n = 7, 63.63%).

ii. Levofloxacin mainly produced lesion on trunk and face (n = 5, 62.5%).

iii. Cotrimoxazole induced FDE lesions in all sites with almost equal frequencies.

iv. Paracetamol was found to preferentially involve the palms and soles (n = 4, 66.67%).

v. Phenytoin induced lesions only on the trunk (n = 5,100 %).

vi. Mucosal FDE:

Oral mucosa [n = 7;9.2%] :

The main drugs incriminated were cotrimoxazole and diclofenac each constituting 2 cases (28.57%). Other offending drugs included metronidazole, doxycycline, levofloxacin and ciprofloxacin, each constituting one case (14.28%). Isolated oral involvement was seen in 5 cases(71.42%). In the mouth, labial mucosa (n = 6, 75%) and hard palate (n = 2, 25%) were involved.

Genital mucosa [n = 7 ;9.2%] :

The main inducers were cotrimoxazole (n = 2, 28.57%) followed by ciprofloxacin, levofloxacin, doxycycline and brufen, in 1 case (14.28%) each. Isolated genital involvement was seen in 4 cases (66.67%). Glans penis was involved in 4 patients (57.14%), scrotum in two patients (28.57%) and vulva in one patient (14.28%).

Others :

- Lips and Perioral area : The frequent inducers were cotrimoxazole and diclofenac contributing to two cases (28.57%) each.

- Periocular involvement was seen in 1 patient (1.31%) due to cotrimoxazole.

DRUG SPECIFIC PATTERN OF INVOLVEMENT (Fig.6):

DRUGS	CLASSICAL (n = 62)				BULLOUS (n = 14)		NONPIGMENTING (n = 1)
	LOCALISED (n = 17)		MUILTIFOCAL (n = 41)	GENERALISED (n = 4)	MUILTIFOCAL (n = 13)	SOLITARY (n = 1)	
	SOLITARY(12)	MULTIPLE(5)					
CIPROFLOXACIN	2	-	4	2	3		
COTRIMOXAZOLE	4	1	1	1	2		
LEVOFLOXACIN	-	-	7	-	1		
DICLOFENAC	2	1	2	-	2		
PARACETAMOL	-	-	2	-	3	1	1
PHENYTOIN	-	-	5	-	-		
DOXYCYCLINE	3	-	1	-	-		
METRONIDAZOLE	-	1	2	1	-		
NORFLOXACIN	-	2	-	-	-		
BRUFEN	-	-	2	-	-		
CARBAMAZEPINE	-	-	1	-	1		
FLUCONAZOLE	-	-	1	-	-		
NIMESULIDE	-	-	1	-	-		
CHLOROQUINE	-	-	1	-	-		
DETAILS UNKNOWN	1	-	11	-	1		

1) CLASSICAL FDE (n = 62, 81.57%) :

- LOCALISED CLASSICAL (n = 17, 22.36%):

- *SOLITARY LOCALISED (n = 12, 15.79%) :*

Cotrimoxazole induced solitary classical FDE lesions in 4 patients (33.33%), followed by doxycycline in 3 patients(25%), diclofenac and ciprofloxacin in 2 patients each(16.67%). The drug detail was unknown in 1 patient.

- *MULTIPLE LOCALISED (n = 5,6.57%) :*

Norfloxacin produced localised multiple FDE lesions on the face in patients (40%).Cotrimoxazole, metronidazole and diclofenac were responsible in 1 case each (20%).

- MULTIFOCAL CLASSICAL (n = 41, 53.95%) :

Most of the multifocal classical FDE lesions were induced by levofloxacin (n = 7,17.07%).The other drugs in the decreasing order of frequency were phenytoin (n = 5, 12.19%), ciprofloxacin (n = 4, 9.75%), paracetamol (n = 3, 7.31%), brufen (n = 2, 4.88%), diclofenac (n = 2, 4.88%), metronidazole (n = 2, 4.88%), carbamazepine (n = 1. 2.44%), chloroquine (n = 1, 2.44%), fluconazole (n = 1, 2.44%) and nimesulide (n = 1, 2.44%). 2 patients with multifocal FDE lesions (more than 15 lesions) were found to be HIV ELISA positive.

- GENERALISED CLASSICAL FDE (n = 4, 5.26%) :

Generalised classical FDE lesions were encountered with ciprofloxacin in 2 cases (50%), cotrimoxazole and carbamazepine in one case each (25%).

2) BULLOUS FDE (n = 14, 18.42%) :

Most of the cases of bullous FDE had multifocal lesions (n = 13, 92.86%) and were attributed to paracetamol (n = 4, 23.08 %) mainly, followed by ciprofloxacin (n = 3, 15.38%), cotrimoxazole (n = 2, 15.38%), diclofenac (n = 2, 15.38%), and carbamazepine (n = 1, 7.14%). The drug details were unknown in one patient (7.14%).

We had one case of solitary bullous FDE on the palms induced by paracetamol. In total, paracetamol was the offender in 4 cases of bullous FDE on the palms and soles (including one case of nonpigmenting bullous FDE).

3) NONPIGMENTING FDE(n = 1, 1.3%) :

There was one case of nonpigmenting bullous FDE on the palms and soles caused by paracetamol.

ASSOCIATED SYMPTOMS :

ASSOCIATED SYMPTOMS	NO : OF PATIENTS
LOCAL :	**n = 60 (78.95%)**
ITCHING	48(80%)
BURNING	12(20%)
ASYMPTOMATIC	16(21.05%)
GENERAL :	**n = 11 (14.47%)**
GENERALISED ITCHING	6(7.89%)
FEVER WITH MYALGIA	3(3.94%)
HEADACHE	2(2.63%)
ABDOMINAL PAIN	2(2.63%)

LOCAL SYMPTOMS :

60 (78.95%) patients had associated local symptoms. 48 of them had itching (80%) and 12(20%) had local burning pain. The lesions were asymptomatic in the rest (21.05%).

GENERAL SYMPTOMS :

11(14.47%) patients had associated constitutional symptoms. Generalised itching was encountered in 6 patients (7.89%). Associated constitutional symptoms were seen in 7 patients (9.21%) during the acute spisodes. 3(3.94%) of them had fever with myalgia, 2 (2.63%) had headache and 2 (2.63%) had abdominal pain with nausea. In all the 7 patients, constitutional symptoms developed only after drug intake and the drugs responsible were prescribed for unrelated complaints.

ROUTINE INVESTIGATIONS :

69 out of 76(90.79%) cases had associated eosinophilia., HIV ELISA was positive in two patients with multifocal classical FDE (2.6%).

DRUG PATCH TEST RESULTS (Fig. 7):

25 out of 64 (32.9%) patients showed positive patch test results. Among these 25 cases, 22 had skin involvement and 3 had mucosal involvement. In all the 22 cases, drug patch testing done on the lesional skin was positive. Except for the 3 cases with mucosal FDE (12%), drug patch testing done on the unaffected skin was found to be negative.

NAME OF THE DRUG	TOTAL NO: OF CASES	PATCH TEST POSITIVE	PATCH TEST NEGATIVE	UNWILLING / LOST FOLLOW
CIPROFLOXACIN(11)	11	4 (36.36%)	7	-
COTRIMOXAZOLE(9)	9	5 (62.5%)	3	1
LEVOFLOXACIN(8)	8	3 (37.5%)	5	-
DICLOFENAC(7)	7	2 (28.5%)	5	-
PARACETAMOL(6)	6	2 (33.33%)	4	-
PHENYTOIN(5)	5	2 (100%)	-	3
DOXYCYCLINE(4)	4	2 (66.67%)	1	1
METRONIDAZOLE(4)	4	1 (25%)	3	-
NORFLOXACIN(2)	2	-	1	1
BRUFEN(2)	2	1 (50%)	-	1
CARBAMAZEPINE(2)	2	1	1	-
CHLOROQUINE(1)	1	1	-	-
FLUCONAZOLE(1)	1	1	-	-
NIMESULIDE(1)	1	1	-	-
DETAILSUNKNOWN(13)	13	-	8	5

- The patch test positivity rate was the highest with doxycycline (66.67%).

- When patch testing was done with cotrimoxazole, Dimethyl sulfoxide was used as vehicle to enhance the positivity of results. The rate of positivity observed was 62.5%.

- With fluoroquinolone group of drugs, the rate of positivity was relatively low. When tested with ciprofloxacin, levofloxacin and norfloxacin, the positivity rates were 36.36%, 37.5% and 0% respectively.

- Patch testing with paracetamol was positive in 33.33% of cases.

- Testing with diclofenac and metronidazole also revealed low rates of positivity (28.5% and 25% respectively).

- Only 4 out of 7 patients in whom anticonvulsants were the main offenders agreed for patch testing. 3(75%) of them showed positive test results.

- 4 (16%) patients had developed delayed positive reactions with negative patch test reading on day 2 and positive test results on day 4.

- Only 8 out of 13 patients who presented with unknown drug history were willing for patch testing. The test result was negative in all of them.

BIOPSY RESULTS

Biopsy was performed in 43.45% (n = 33) of patients ; 44.7% of patients refused biopsy and 11.8% of patients had lost follow up. Out of the 33 willing patients, 15 (45.45%) had acute lesions. The remaining 18 (54.55%) had residual hyperpigmented patch. The histopathological findings were consistent with FDE in all of them.

In patients with acute classical lesions the following findings were recorded :

Epidermal spongiosis was seen in 10 patients (66.67%). Basal cell degeneration with necrotic keratinocytes and few dermal melanophages was seen in all of them. The papillary dermis showed dense band of inflammatory infiltrates in close approximation to the basal layer in 12 patients (80%).The infiltrates were less dense in the rest (20%). Perivascular inflammatory infiltrates were seen in all of them. Few cases showed an admixture of eosinophils and neutrophils in the dermis. In patients with bullous FDE, a sub epidermal bulla was seen in addition.

In long standing cases (n=18) with residual hyperpigmentation, the infiltrates were relatively less dense when compared to acute lesions. The density of melanophages was variable. When compared to acute lesions, the density of melanophages was found to be greater in chronic lesions. There was an intense density of melanophages in the upper dermis in two patients (11.11%).

IMMUNOHISTOCHEMICAL ANALYSIS

Immunohistochemical analysis using anti CD8 antibodies was done in 8 cases (4 with acute FDE lesion and 4 with residual hyperpigmentation). The presence of CD8+ T-cells was demonstrated in all of them. The specimen from acute cases showed dense focal collection of CD8+ T-cells at the sites of FDE lesions. In all the 4 patients, the upper dermis showed collection of CD8+ T-cells. The intraepidermal collection was found to be sparse in all the 4 cases. Immunohistochemistry of biopsy specimen from chronic cases showed few, sparse CD8+ resting T-cells in the upper dermis.

DISCUSSION

In our study the incidence of Fixed drug eruption was found to be 0.54% among Dermatology OPD attendees. The incidence from different reports seems to vary from 2.5% to as high as 22%[10,11]. Factors like geographic area, availability of drugs and their usage, age group, literacy status, socioeconomic factors, availability of over the counter medications etc affect the incidence of FDE[10].

FDE was the second common cutaneous adverse drug reaction pattern (23.47%) encountered. Maculopapular rash was the most common CADR pattern observed in 29.25% of cases. However, according to many Indian studies, FDE is the most common CADR observed[12,13]. One study from North India[17] and studies from western world[16,17] have produced similar results.

Our study reflects a broad patient age range from 8 months to 75 years. The main age group affected in our study was 21-30 years. This is in accordance with the previous studies on FDE, conducted in Pakistan by Mahboob and Haroon[40] and in Nigeria by Nnoruka[72]. The opportunity for exposure to drugs causing FDE is probably high in this age group. However all age groups are vulnerable to FDE.

The male to female ratio in our study was 1.23:1. The slight male preponderance did not reveal any statistical significance. The occurrence of FDE appeared to be almost equal in both sexes .This is in concordance with few previous studies - Mahoob et al reported a sex incidence of 1.1:1[40] and Nnoruka et al[72] reported a sex incidence of 1.3:1 in their respective studies. However, earlier studies showed a male preponderance[10,11]. A recent 3 year analysis of FDE lesions in hospital settings in France done by Brahimi N showed controversial results. Females were frequently affected with late age at presentation of FDE[184].

In our study there was no report of occurrence of FDE following intake of indigenous medicine. None of our patients had family history of drug allergy. There was no personal or family history of atopy in any of them. The occurrence of FDE in atopic individuals has been reported by Mahboob and Taroon[40].

14% of patients had FDE for the first time. This is in conformity with the previous studies done by Mahboob et al and Nnoruka et al (13.3% and 19% respectively)[40,72]. 13% had suffered more than 5 episodes of FDE. Most of them had attended our OPD for other dermatological problems. The patients with recurrent episodes were not bothered of their.

In the current study, the mean time interval between drug exposure and occurrence of FDE during the first episode was 13.14 days and that during subsequent episodes was 4.65 hours respectively. The difference in time interval was found to be statistically significant. During recurrent episodes, FDE was found to occur as early as 20 minutes in our study. The incubation period observed in our study, during the initial and subsequent episodes correlates well with the time period quoted in literature[4,39]. It takes a few weeks for sensitisation to occur to a particular drug initially. Once sensitisation occurs, the resting memory CD8+ T-cells get reactivated on subsequent drug exposures and produce the lesions within a few minutes to hours, representing a form of recall phenomenon.

The common morphological pattern described by all previous studies is an erythematous macule evolving into an edematous plaque subsiding with residual hyperpigmentation. In the current study, this classical presentation was seen in 81.57% of cases. 2 other clinical patterns encountered were Bullous FDE(18.42%) and Nonpigmenting FDE(1.3%).

Multifocal or scattered pattern of distribution was the most frequent pattern seen in our patients. The pattern of distribution of lesions ranged between solitary and generalised involvement. Extensive and

generalised involvement seen in 5.3% of cases necessitates the importance of early detection of the responsible drug. Hospital admission is necessary for these patients as this form of FDE closely mimics SJS and TEN[125-127].

In our study, the largest size of FDE lesion seen was 15cms. Though circular lesions were very common, irregular patches and polycyclic lesions were also seen. The occurrence of polycyclic lesions is very rare and was first reported by Mahboob and Haroon in Pakistan[40]. These lesions are seen in cases with recurrent episodes, where the individual lesions fuse together to produce polycyclic forms.

The most common causes of FDE varied according to the various geographic areas. The true incidence of FDE for a particular drug depends on the frequency of its use [10]. In developing countries like ours, the problem is further compounded because of the availability of over the counter medications and indigenous drug preparations. Despite all these factors, the most common drug incriminated according to various study reports from India[12,185], Turkey, Pakistan[40] and Libya[186] was cotrimoxazole. Antimalarials (pyrimethamine and sulfamethoxazole) were the most common inducers in a study done in Nigeria[72]. According to the study conducted by Brahimi N in France[184], paracetamol was the most common offending drug. Tetracyclines were the main offenders in

a study conducted in Singapore by Chan[187]. Compared with previous reports, the causative drugs varied from decade to decade. In our study, fluoroquinolones were the major culprits contributing to 27.63% of cases. The main inducers in this group were ciprofloxacin (14.48%) and levofloxacin (10.53%). So far no other studies have cited these group of drugs as the most common offenders. The great majority of reports of FDE due to fluoroquinolones have been recent. S.Dhar has described 7 cases with FDE to ciprofloxacin in 1996[188]. In his study, he has quoted that, with widespread use, ciprofloxacin could become one of the common drugs causing FDE in future. The findings in our study have justified this statement.

Cotrimoxazole was the second common inducer next to ciprofloxacin, responsible for 11.84% of FDE cases. Nearly half of the patients (4/9) were children less than 14 years of age .This is attributed to the increased rate of prescription of cotrimoxazole for pediatric patients in government hospitals. Owing to the increased occurrence of drug allergies to sulphonamides, private medical practitioners are hesitant to prescribe this group of drugs nowadays. In our study, the other antibacterials that need special mention include norfloxacin, metronidazole and doxycyline.

Nonsteroidal anti-inflammatory drugs were the second important offending group of drugs with diclofenac topping the list. Diclofenac is the most commonly prescribed drug for myalgia and arthralgia in out patient departments. However the reports of FDE occurring to diclofenac are relatively few. FDE to diclofenac was first reported in 1998 by Mahboob and Taroon[40]. Paracetamol, the most frequently prescribed over the counter drug, was responsible in 7.89% of cases. There was one case in our study, related to nimesulide intake. So far very few cases of FDE occuring to nimesulide have been reported in literature[79,189]. Among the anticonvulsants, the main offender was phenytoin(5.6%). The other less common inducer was carbamazepine. There are recent reports of increased cross sensitivity and polysensitivity among these group of drugs[87]. This fact should be kept in mind while deciding on alternate drugs.

Regarding the drug specific pattern of involvement, bullous FDE was mainly attributed to ciprofloxacin involving 28.57% of cases. There are a few reports of multifocal or generalised bullous eruptions to ciprofloxacin available in literature[58,125]. Other drugs that resulted in the causation of bullous FDE were paracetamol (21.42%), cotrimoxazole (14.28%), diclofenac (14.28%) carbamazepine (7.14%) and levofloxacin

(7.14%). Bullous FDE to cotrimoxazole, diclofenac and paracetamol have already been reported across the world[75,116,122].

The nonpigmenting variant of FDE has been mainly reported to occur with pseudoephedrine and phenylpropanolamine[106]. Few cases of NPFDE occurring to paracetamol have been reported so far across the world[134]. In our patient, paracetamol induced nonpigmenting bullous FDE on the palms and soles .

The previous studies analysing the most frequently involved sites have produced varied results. In studies conducted by S. Dhar and Mahboob[40], extremities were the most common sites affected. However, in a study conducted by Ozkaya Bayazit, genitalia was the most common affected site[46]. In our study, extremities (44.73%) was the most frequent site of involvement. The other sites affected, in decreasing order of frequencies were trunk, face, oral mucosa, genitalia and palms and soles.

There was no statistically significant association between FDE inducing drugs and FDE sites in our study, as the sample size in most of categories was relatively small. However clinical relevance was seen in few cluster groups. In all the 5 cases involved, phenytoin induced lesions exclusively on the trunk(100%). Ciprofloxacin preferably induced lesions on the extremities in 63.63% of cases. Levofloxacin mainly produced

lesions on the trunk and face. Cotrimoxazole, as shown in previous studies[46,50], is capable of inducing FDE on any site including extremities, trunk, face, lips, oral and genital mucosa. Paracetamol was mainly found to involve the palms and soles (66.67%).

In our study, face involvement was more commonly encountered with diclofenac. Lip involvement was mainly seen with drugs like cotrimoxazole and diclofenac. In previous studies, lip involvement was mainly attributed to cotrimoxazole and pyrazolone group of drugs[46,50].

In our patients, oral mucosal involvement occurred mainly with cotrimoxazole and diclofenac (28.57% each). In a study of FDE on the oral mucosa conducted by V.K.Jain, tetracyclines, cotrimoxazole and oxyphenbutazone were the most common causative drugs[45]. Genital involvement was mainly caused by cotrimoxazole and fluoroquinolones. Genital FDE to fluoroquinolones are very rarely reported in literature. FDE exclusively involving the genitalia of 60 male patients were investigated by Pandhi R K in 1984[190]. Tetracyclines, aspirin, metamizole and cotrimoxazole were the common etiological agents. Though stastistically insignificant, the clinical pattern and distribution of lesions in FDE seem to be influenced by the drug in question, and the study of pattern may provide useful information in selecting the most likely causative drug, especially when the details of the drugs are unknown.

The rate of occurrence of local symptoms at the site of FDE lesions was as low as 28% in previous studies[40]. Our study revealed a rate of 78.95%, which is quite high. The symptoms appreciated were in the form of local itching and burning pain. Systemic symptoms in the form of generalised itching, fever with myalgia, headache and abdominal pain with nausea were found to be associated in 14.47% of patients. In previous studies,the reported incidence of systemic symptoms was as low as 1%[40].

Eosinophilia was seen in 90.79% of cases which is significantly high. It is not known whether patients with eosinophilia are more prone to develop FDE . This finding needs to be evaluated by further studies in future. In our study, HIV ELISA was positive in two patients.

In the present study, the patch testing done to confirm the causality of the offending drugs showed positivity on the lesional skin when compared to the nonlesional skin. This finding is concordant with the results obtained from other studies[190].

The willingness to undergo patch testing was obtained only in 64 patients. Patients who were willing for biopsy were not willing for patch testing and vice versa. Nearly half of the patients with FDE to

anticonvulsant drugs were unwilling as they had a false belief that their seizures could get precipitated as a result of patch testing.

In our study, drug patch testing showed a low rate of positivity (32.9%), when compared to few previous studies[158,162]. This is attributed to the following reasons :

- The rate of negativity was high among the patients who presented with unknown drug details
- Many of the patients with negative test results were manual labourers and farmers who worked for daily wages. They were not able to refrain themselves from strenuous activities.
- Positive test results were obtained in 4 patients when the reading was taken on day 4. Not all patients were willing to report back on day 4.
- Patients were hesitant to come back for repeat application test or for repeat patch testing with increasing concentration of drugs.

Biopsy was performed in 43.45% of willing patients. Classical histopathological features were seen in both acute and chronic cases. In acute cases epidermal spongiosis, basal cell degeneration and

inflammatory infiltrares in the upper dermis were more pronounced. Dermal melanophages were few. In chronic FDE the infiltrates were less dense. The density of melanophages was relatively high. Many patients with mucosal FDE and with FDE lesions on the face refused biopsy.

As immunohistochemical analysis was expensive, the CD8 marker study was performed only in 8 cases (4 acute and 4 chronic). Both acute and chronic lesions showed CD8 positivity, though the density of cells varied between acute and chronic lesions. Acute lesions revealed the presence of a few intraepidermal T-cells close to the basal keratinocytes. These findings clearly reveal the persistence of CD8+ T-cells at the sites of FDE, even after resolution of lesions. These resident population of T-cells contribute to the occurrence of lesions at the same site after reexposure to the offending drugs.

LIMITATIONS OF THE STUDY

- Approval could not be obtained for oral provocation test, the gold standard test done to confirm the causative drug. The confirmation of the drugs incriminated in causation of FDE through patch testing was not possible in all cases.

- A statistically significant relation between the offendings drugs and drug specific site of involvement could not be established owing to small sample size.

- Regular follow up of cases was not possible.

- Immunohistochemical analysis to identify CD8+ T-cells in the FDE lesions was not done in all cases due to financial limitations.

CONCLUSION

1. The incidence of Fixed Drug Eruption among Dermatology OPD attendees from Aug 2008 to Aug 2010 was found to be 0.54%.

2. The main age group affected was 21 – 30 years.

3. An almost equal sex incidence. was observed with the male to female ratio being 1.23:1.

4. The incubation period observed during the first and subsequent episodes was 13.4 days and 4.6hrs respectively.

5. The most common offenders were fluoroquinolones especially ciprofloxacin seen in 14.5% of cases and levofloxacin in 10.5% of cases. The next common offender was cotrimoxazole inducing FDE in 11.8% of cases. Nonsteroidal antiinflammatory drugs were the causative drugs in 19.73% of cases with diclofenac being the main inducer followed by paracetamol.

6. Classical presentation was seen in 81.57% of cases. The other two morphological patterns encountered were Bullous FDE(18.42%) and Nonpigmenting FDE(1.33%).

7. Multifocal pattern was the most common pattern of distribution of lesions. Solitary and generalised patterns were also encountered.

8. Extremities were the most frequently involved sites seen in 44.73% of cases, followed in decreasing order of frequency by trunk, face, oral mucosa, genital mucosa, lips and palms and soles.

9. There was no statistically significant difference between males and females regarding the site of involvement . Clinically mucosal lesions and lesions on the palms and soles were more commonly encountered in males. Involvement of the lip was commonly seen in females.

10. Though statistically insignificant, clinically significant associations were observed regarding drug specific site of involvement. Phenytoin induced FDE exclusively on the trunk. Paracetamol was observed to induce bullous FDE preferentially on palms and soles Ciprofloxacin induced lesions mainly on the extremities.

11. The rate of occurrence of associated local and systemic symptoms was 78.95% and 14.47% respectively which is relatively high when compared to previous studies.

12. Drug patch tests done to establish the causality of offending drugs revealed positivity in 32.9% of patients. The testing was found to be positive when done on lesional skin when compared to nonlesional skin.

13. Histopathological examination of biopsy specimens produced consististent findings in all the 33 cases in whom biopsy was performed.

14. Immunohistochemical analysis done using antibodies to CD8 revealed positivity in both acute and chronic cases, establishing the role of these cells in causation of FDE.

In the current study, the number of patients observed was less when compared to the previous studies. So statistical analysis did not reveal any significance regarding the sex specific and drug specific site of involvement.

To conclude, in most cases, fixed drug eruption poses a great challenge for the physician to reveal the offending agent, especially when patients have a multidrug history and do not remember which drug they have taken. Large scale studies investigating the drug specific site of involvement in FDE should be carried out in future, so that the offending drugs can be identified to some extent based on the site of occurrence of

lesions. Regularly updated lists of the most frequent FDE inducers in a given community should be made available.

Patch testing which is standardised for the diagnosis of allergic contact dermatitis is often useful for the diagnosis of offending drugs in FDE. As there are differences in the clinical and pathophysiological aspects of these two disorders, this technique has to be adapted to the study of FDE, so that we can retrieve more specific and sensitive results. Subjective symptoms such as local itching and burning can also be considered as a positive test result. Oral provocation test should be considered only after analysis of the risk- benefit ratio in a patient.

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MASTER CHART

SL. NO	SEX	DRUG HISTORY	NO:OF EPISODES	TIME INTERVAL BETWEEN DRUG INTAKE & ONSET OF LESION	PATTERN OF INVOLVEMENT	SITE OF INVOLVEMENT	CBC	PATCH TESTING	BIOPSY
1.	M	CIPROFLOXACIN	1	12 DAYS	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
2.	M	DICLOFENAC	2	1 Hr	CLASSICAL MUCOSAL	ORAL MUCOSA	EOSINOPHILIA	NEGATIVE	NOT WILLING
3.	F	DICLOFENAC	1	10 DAYS	SOLITARY CLASSICAL	TRUNK	EOSINOPHILIA	NEGATIVE	CONSISTENT
4.	F	LEVOFLOXACIN	3	1 Hr	MULTIFOCAL CLASSICAL	FACE, EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
5.	F	COTRIMOXAZOLE	1	7 DAYS	MULTIFOCAL CLASSICAL	FACE, LIPS,PERIORAL	NORMAL	POSITIVE	NOT WILLING
6.	M	DOXYCYCLINE	2	30 Min	CLASSICAL MUCOSAL	GENITAL	EOSINOPHILIA	NEGATIVE	CONSISTENT
7.	F	CHLOROQUINE	3	1 HR	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	POSITIVE	CONSISTENT
8.	M	PARACETAMOL	1	8 DAYS	BULLOUS	PALMS & SOLES	EOSINOPHILIA	POSITIVE	NOT WILLING
9.	M	FLUCONAZOLE	2	4 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	POSITIVE	NOT WILLING
10.	M	CIPROFLOXACIN	3	3 Hrs	BULLOUS	EXTREMITIES	EOSINOPHILIA	NEGATIVE	NOT WILLING
11.	F	DICLOFENAC	4	4 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES, TRUNK	EOSINOPHILIA	NEGATIVE	CONSISTENT
12.	F	DETAILS UNKNOWN	2	2 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	NORMAL	NEGATIVE	CONSISTENT
13.	M	CIPROFLOXACIN	2	1 Hr	GENERALISED CLASSICAL	FACE, TRUNK, EXTREMITIES	EOSINOPHILIA	POSITIVE	NOT WILLING
14.	F	DETAILS UNKNOWN	2	1 Hr	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
15.	M	BRUFEN	6	30 Min	MULTIFOCAL CLASSICAL	EXTREMITIES,GENITALIA	EOSINOPHILIA	NEGATIVE	NOT WILLING
16.	M	DETAILS UNKNOWN	2	8 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES,GENITALIA	EOSINOPHILIA	NEGATIVE	CONSISTENT
17.	F	LEVOFLOXACIN	1	14 DAYS	CLASSICAL MUCOSAL	ORAL MUCOSA, GENITALIA	NORMAL	POSITIVE	NOT WILLING
18.	F	DETAILS UNKNOWN	3	6 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	NOT WILLING	CONSISTENT
19.	M	CIPROFLOXACIN	6	5 Hrs	CLASSICAL MUCOSAL	GENITAL	NORMAL	NEGATIVE	CONSISTENT
20.	M	DETAILS UNKNOWN	7	4-5 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
21.	M	DICLOFENAC	3	1 Hr	BULLOUS	TRUNK	EOSINOPHILIA	POSITIVE	NOT WILLING
22.	F	DETAILS UNKNOWN	1	>10 DAYS	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	NOT WILLING
23.	M	PARACETAMOL	5	1 Hr	BULLOUS	PALMS,SOLES,EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
24.	M	METRONIDAZOLE	2	6 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	NEGATIVE	CONSISTENT
25.	F	CARBAMAZEPINE	2	6 Hrs	BULLOUS	EXTREMITIES	EOSINOPHILIA	POSITIVE	CONSISTENT
26.	M	CIPROFLOXACIN	3	8 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	NEGATIVE	NOT WILLING

SL. NO	SEX	DRUG HISTORY	NO:OF EPISODES	TIME INTERVAL BETWEEN DRUG INTAKE & ONSET OF LESION	PATTERN OF INVOLVEMENT	SITE OF INVOLVEMENT	CBC	PATCH TESTING	BIOPSY
27.	M	CARBAMAZEPINE	5	2 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	NOT WILLING	NOT WILLING
28.	F	DETAILS UNKNOWN	2	2 Hrs	BULLOUS	TRUNK	EOSINOPHILIA	LOST FOLLOW UP	LOST FOLLOW UP
29.	F	CIPROFLOXACIN	3	1 Hr	BULLOUS	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
30.	F	CIPROFLOXACIN	2	30 Min	CLASSICAL MUCOSAL	ORAL MUCOSA	EOSINOPHILIA	POSITIVE	NOT WILLING
31.	M	COTRIMOXAZOLE	1	21 Days	BULLOUS	TRUNK	EOSINOPHILIA	NEGATIVE	CONSISTENT
32.	M	DICLOFENAC	6	2 Hrs	MULTIFOCAL CLASSICAL	PALMS	EOSINOPHILIA	POSITIVE	NOT WILLING
33.	F	NORFLOXACIN	2	48 Hrs	LOCALISED CLASSICAL	FACE	NORMAL	NEGATIVE	NOT WILLING
34.	M	PHENYTOIN	4	8 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	POSITIVE	NOT WILLING
35.	F	CIPROFLOXACIN	2	7 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	NEGATIVE	CONSISTENT
36.	M	CIPROFLOXACIN	3	5 Hrs	BULLOUS	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
37.	F	PHENYTOIN	4	4 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	NOT WILLING	NOT WILLING
38.	M	DICLOFENAC	10	30 Min	CLASSICAL MUCOSAL	ORAL MUCOSA, FACE,LIPS	NORMAL	NEGATIVE	NOT WILLING
39.	M	LEVOFLOXACIN	3	3 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
40.	F	COTRIMOXAZOLE	3	8 Hrs	GENERALISED CLASSICAL	FACE, LIPS,EXTREMITIES, TRUNK	EOSINOPHILIA	POSITIVE	CONSISTENT
41.	F	DETAILS UNKNOWN	2	4 Hrs	SOLITARY CLASSICAL	TRUNK	EOSINOPHILIA	NEGATIVE	NOT WILLING
42.	M	NIMESULIDE	1	22 Days	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	POSITIVE	NOT WILLING
43.	M	LEVOFLOXACIN	2	6 Hrs	MULTIFOCAL CLASSICAL	FACE, TRUNK	EOSINOPHILIA	POSITIVE	LOST FOLLOW UP
44.	M	COTRIMOXAZOLE	2	4 Hrs	CLASSICAL MUCOSAL	GENITAL	EOSINOPHILIA	NEGATIVE	LOST FOLLOW UP
45.	F	DETAILS UNKNOWN	3	6 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES, FACE,PERIORAL	EOSINOPHILIA	LOST FOLLOW UP	LOST FOLLOW UP
46.	M	BRUFEN	9	2 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NOT WILLING	NOT WILLING
47.	F	PARACETAMOL	2	30-45 Min	BULLOUS	PALMS	EOSINOPHILIA	POSITIVE	NOT WILLING
48.	M	DOXYCYCLINE	2	2 Hrs	LOCALISED CLASSICAL	FACE	EOSINOPHILIA	NOT WILLING	NOT WILLING
49.	F	COTRIMOXAZOLE	1	14 Days	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	POSITIVE	CONSISTENT
50.	M	NORFLOXACIN	2	8 Hrs	LOCALISED CLASSICAL	FACE, PERIORAL	EOSINOPHILIA	POSITIVE	NOT WILLING
51.	M	PHENYTOIN	2	8 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	LOST FOLLOW UP	LOST FOLLOW UP
52.	F	DOXYCYCLINE	2	10 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	POSITIVE	CONSISTENT

SL. NO	SEX	DRUG HISTORY	NO:OF EPISODES	TIME INTERVAL BETWEEN DRUG INTAKE & ONSET OF LESION	PATTERN OF INVOLVEMENT	SITE OF INVOLVEMENT	CBC	PATCH TESTING	BIOPSY
53.	M	COTRIMOXAZOLE	1	15 Days	BULLOUS	TRUNK	EOSINOPHILIA	NEGATIVE	CONSISTENT
54.	F	LEVOFLOXACIN	3	24 Hrs	MULTIFOCAL CLASSICAL	FACE, TRUNK	EOSINOPHILIA	NEGATIVE	NOT WILLING
55.	M	DETAILS UNKNOWN	5	2 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	LOST FOLLOW UP	LOST FOLLOW UP
56.	M	PHENYTOIN	3	24 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	LOST FOLLOW UP	LOST FOLLOW UP
57.	F	CIPROFLOXACIN	6	6-8 Hrs	GENERALISED CLASSICAL	FACE, LIPSTRUNK , EXTREMITIES,PERIORAL	EOSINOPHILIA	POSITIVE	NOT WILLING
58.	F	DETAILS UNKNOWN	1	18 Days	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
59.	M	PARACETAMOL	2	30 Min	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
60.	M	METRONIDAZOLE	2	1 Hr	GENERALISED CLASSICAL	TRUNK, FACE, ORAL, PALMS	EOSINOPHILIA	POSITIVE	CONSISTENT
61.	F	LEVOFLOXACIN	2	1 Hr	MULTIFOCAL CLASSICAL	FACE,EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
62.	M	DETAILS UNKNOWN	5	1 Hr	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	LOST FOLLOW UP	LOST FOLLOW UP
63.	M	COTRIMOXAZOLE	3	24 Hrs	CLASSICAL MUCOSAL	ORAL MUCOSA	EOSINOPHILIA	NEGATIVE	CONSISTENT
64.	F	LEVOFLOXACIN	1	10 Days	BULLOUS	FACE, EXTRMITIES	EOSINOPHILIA	POSITIVE	NOT WILLING
65.	F	DETAILS UNKNOWN	6	12 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	NOT WILLING
66.	M	PARACETAMOL	2	8 Hrs	BULLOUS	PALMS, EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
67.	F	METRONIDAZOLE	2	6 Hrs	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	NEGATIVE	CONSISTENT
68.	M	DOXYCYCLINE	2	1 Hr	CLASSICAL MUCOSAL	ORAL MUCOSA	EOSINOPHILIA	POSITIVE	NOT WILLING
69.	M	CIPROFLOXACIN	1	8 Days	BULLOUS	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
70.	F	PHENYTOIN	5	1 Hr	MULTIFOCAL CLASSICAL	TRUNK	EOSINOPHILIA	POSITIVE	NOT WILLING
71.	M	COTRIMOXAZOLE	1	15 Days	CLASSICALMUCOSAL	ORAL MUCOSA	EOSINOPHILIA	NOT WILLING	LOST FOLLOW UP
72.	F	PARACETAMOL	6	1 Hr	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT
73.	M	METRONIDAZOLE	6	20 Min	LOCALISED CLASSICAL	FACE	EOSINOPHILIA	POSITIVE	NOT WILLING
74.	M	COTRIMOXAZOLE	2	2 Hrs	CLASSICAL MUCOSAL	GENITAL	EOSINOPHILIA	NEGATIVE	NOT WILLING
75.	F	DICLOFENAC	7	4 Hrs	BULLOUS	TRUNK, FACE,PERIORAL, LIPS	EOSINOPHILIA	POSITIVE	NOT WILLING
76.	F	LEVOFLOXACIN	2	2 Hrs	MULTIFOCAL CLASSICAL	EXTREMITIES	EOSINOPHILIA	NEGATIVE	CONSISTENT

PROFORMA

NAME :

AGE :

SEX :

OCCUPATION :

OUTPATIENT NUMBER :

ADDRESS :

RELEVANT HISTORY :

1. Nature of the drug	-	Allopathy / Others
2. Single or Multiple	:	
3. Name of the drug/drugs	:	
4. Purpose of drug untake	:	
5. Number of episodes	-	First
	-	Recurrent(specify number)
6. Duration of lesions	:	
7. Time interval between drug intake and onset of lesions	:	
8. Site of occurrence	:	
9. Nature of lesions	:	Reddish flat / Reddish swollen / Fluid filled / pigmented
10. Residual lesion	:	Pigmenting/nonpigmenting
11. Ass local symptoms	:	Itching/Burning/Itching & burning
12. Ass systemic symptoms	:	Generalised itching / Fever / arthralgia / Myalgia / Nausea, Vomitting / Disorientation
13. Past history	:	H/o atopy
		H/o DM/HT/TB/BA

14. Personal history :

15.Sexual history :

16.Family history of drug allergy:

GENERAL EXAMINATION :

Level of consciousness

Orientation

Anemia/Jaundice/Cyanosis

Body temperature

Lymph nodes

Pulse rate

Blood pressure

SYSTEMIC EXAMINATION :

CVS :

RS :

ABD :

CNS :

DERMATOLOGICAL EXAMINATION :

SKIN :

Morphological pattern of disease :

CLASSICAL/BULLOUS/OTHERS

Site of lesions :

Number of lesions :

MUCOSA :

PALMS AND SOLES :

HAIR & NAILS :

INVESTIGATIONS :

HEMATOLOGICAL :

Complete Blood Count : Total count

Differential count

ESR

Absolute Eosinophil count :

BLOOD VDRL & HIV ELISA :

BIOPSY AND HISTOPATHOLOGICAL EXAMINATION :

PATCH TESTING WITH COMMERCIALISED DRUG FORM :

LESIONAL SKIN :

NONLESIONAL SKIN :

IMMUNOHISTOCHEMISTRY(CD8) :

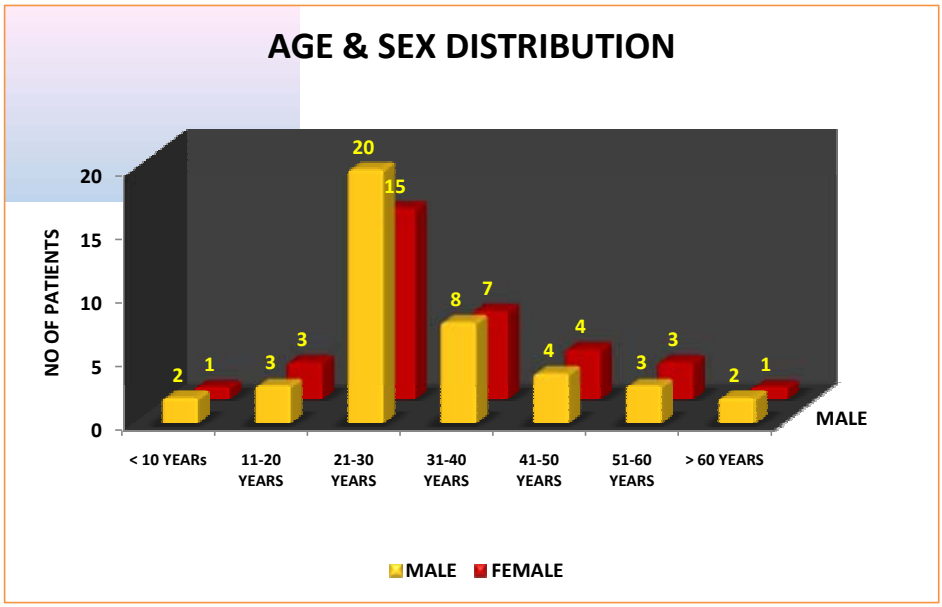


Figure 1

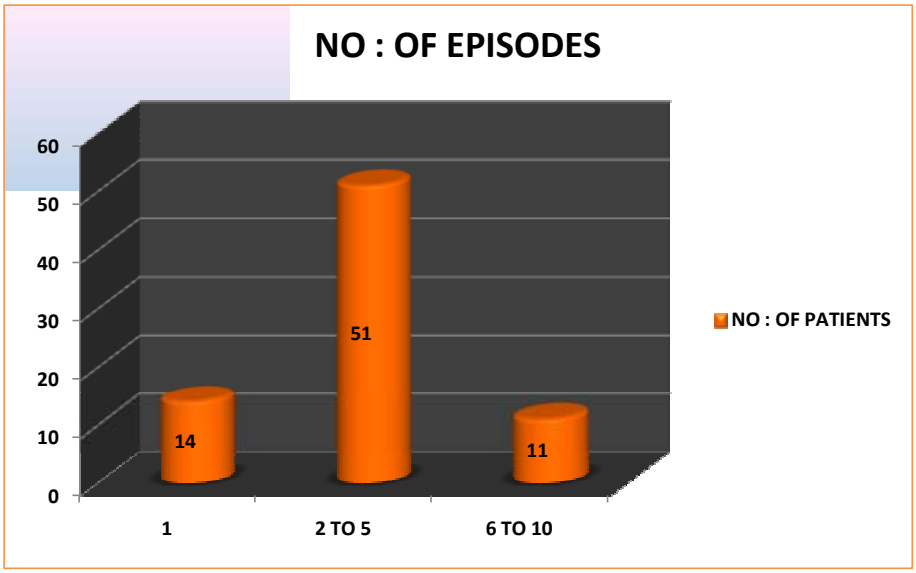


Figure 2

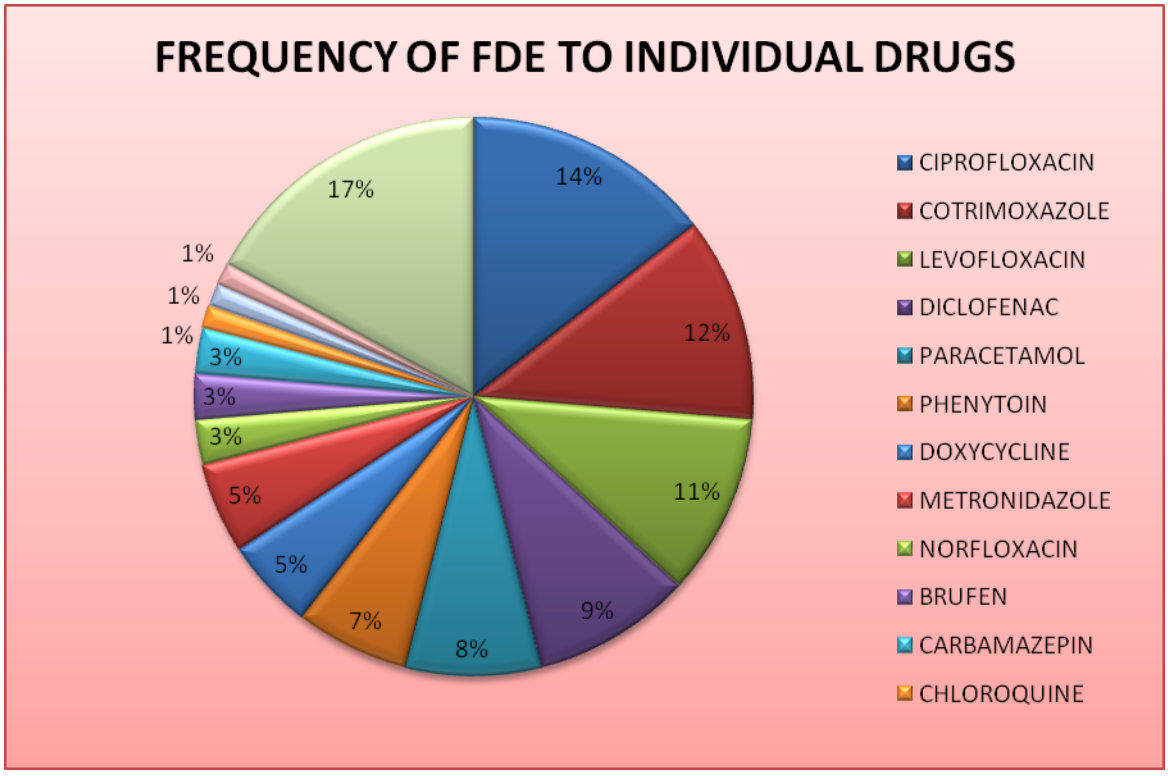


Figure3

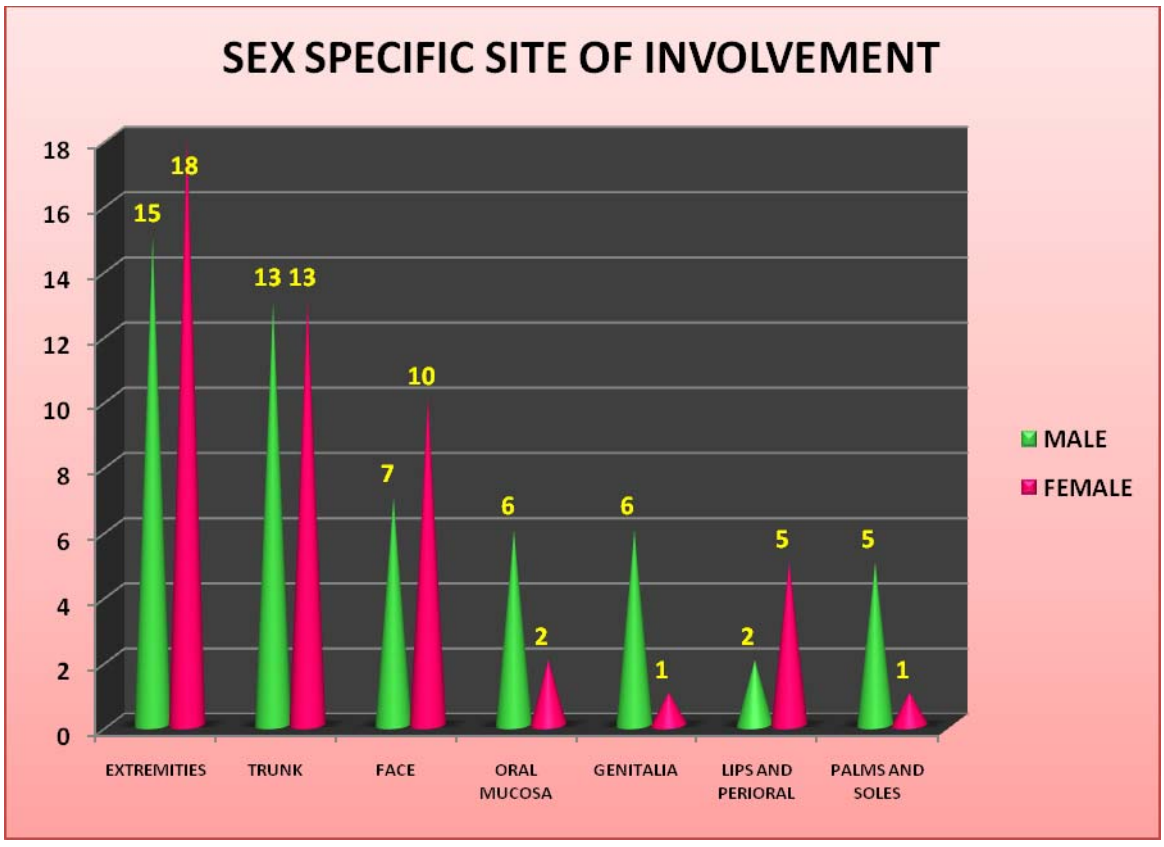


Figure 4

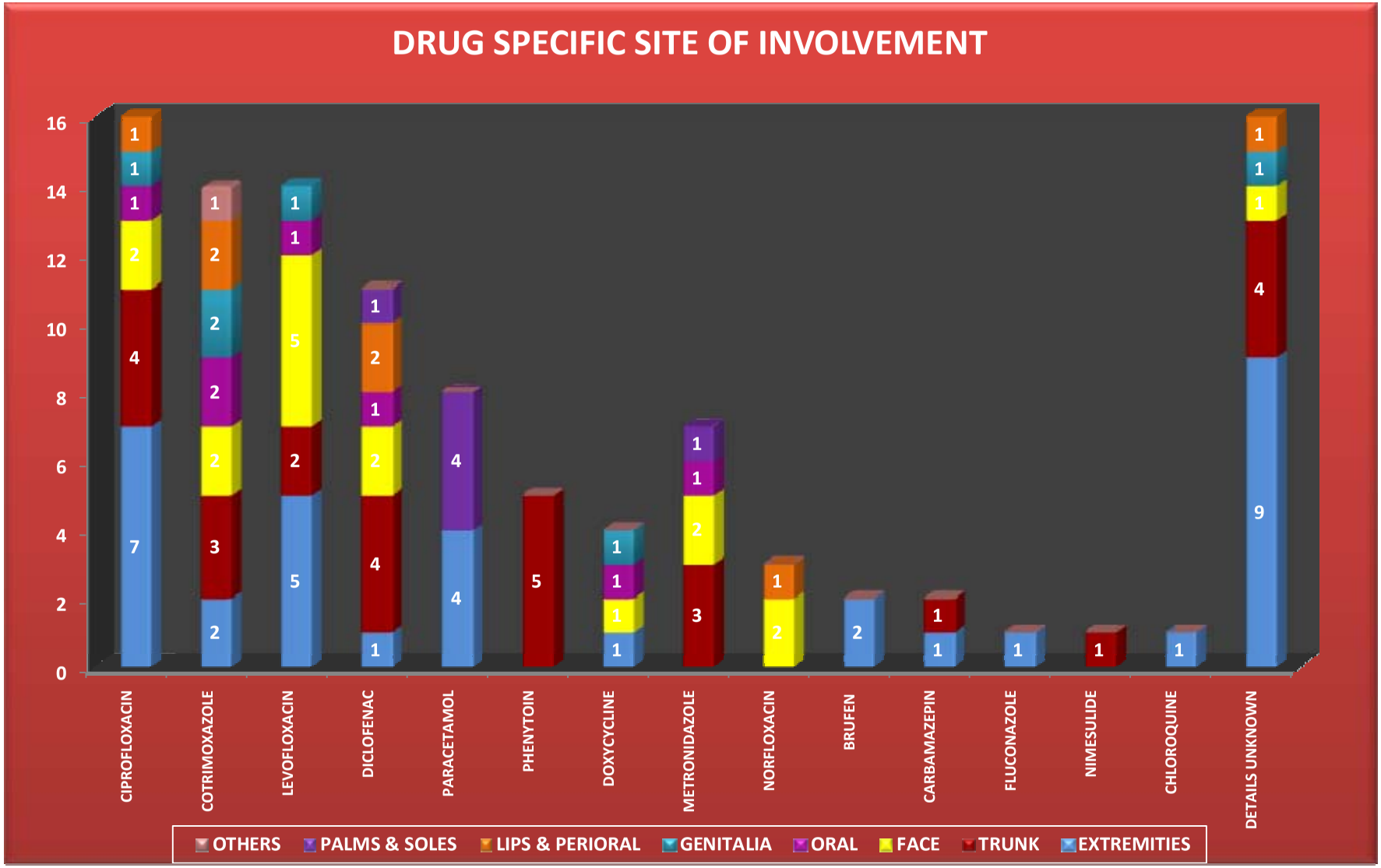

DRUG SPECIFIC SITE OF INVOLVEMENT
16
14
12
10
8
6
4
2
0
CIPROFLOXACIN
COTRIMOXAZOLE
LEVOFLOXACIN
DICLOFENAC
PARACETAMOL
PHENYTOIN
DOXYCYCLINE
METRONIDAZOLE
NORFLOXACIN
BRUFEN
CARBAMAZEPIN
FLUCONAZOLE
NIMESULIDE
CHLOROQUINE
DETAILS UNKNOWN
OTHERS
PALMS & SOLES
LIPS & PERIORAL
GENITALIA
ORAL
FACE
TRUNK
EXTREMITIES

Figure 5

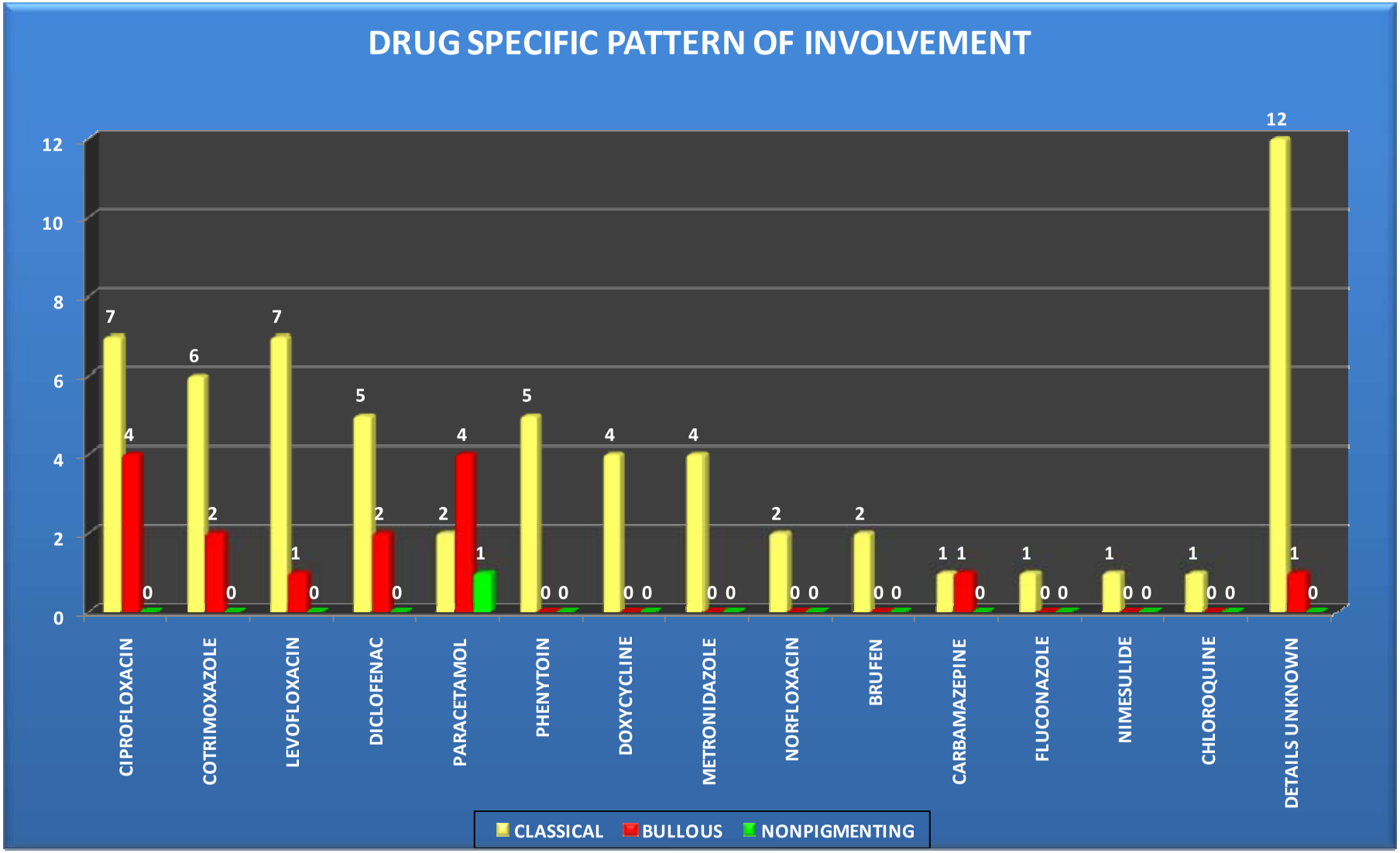

DRUG SPECIFIC PATTERN OF INVOLVEMENT
12
10
8
6
4
2
0
CIPROFLOXACIN
COTRIMOXAZOLE
LEVOFLOXACIN
DICLOFENAC
PARACETAMOL
PHENYTOIN
DOXYCYCLINE
METRONIDAZOLE
NORFLOXACIN
BRUFEN
CARBAMAZEPINE
FLUCONAZOLE
NIMESULIDE
CHLOROQUINE
DETAILS UNKNOWN
CLASSICAL
BULLOUS
NONPIGMENTING

Figure 6

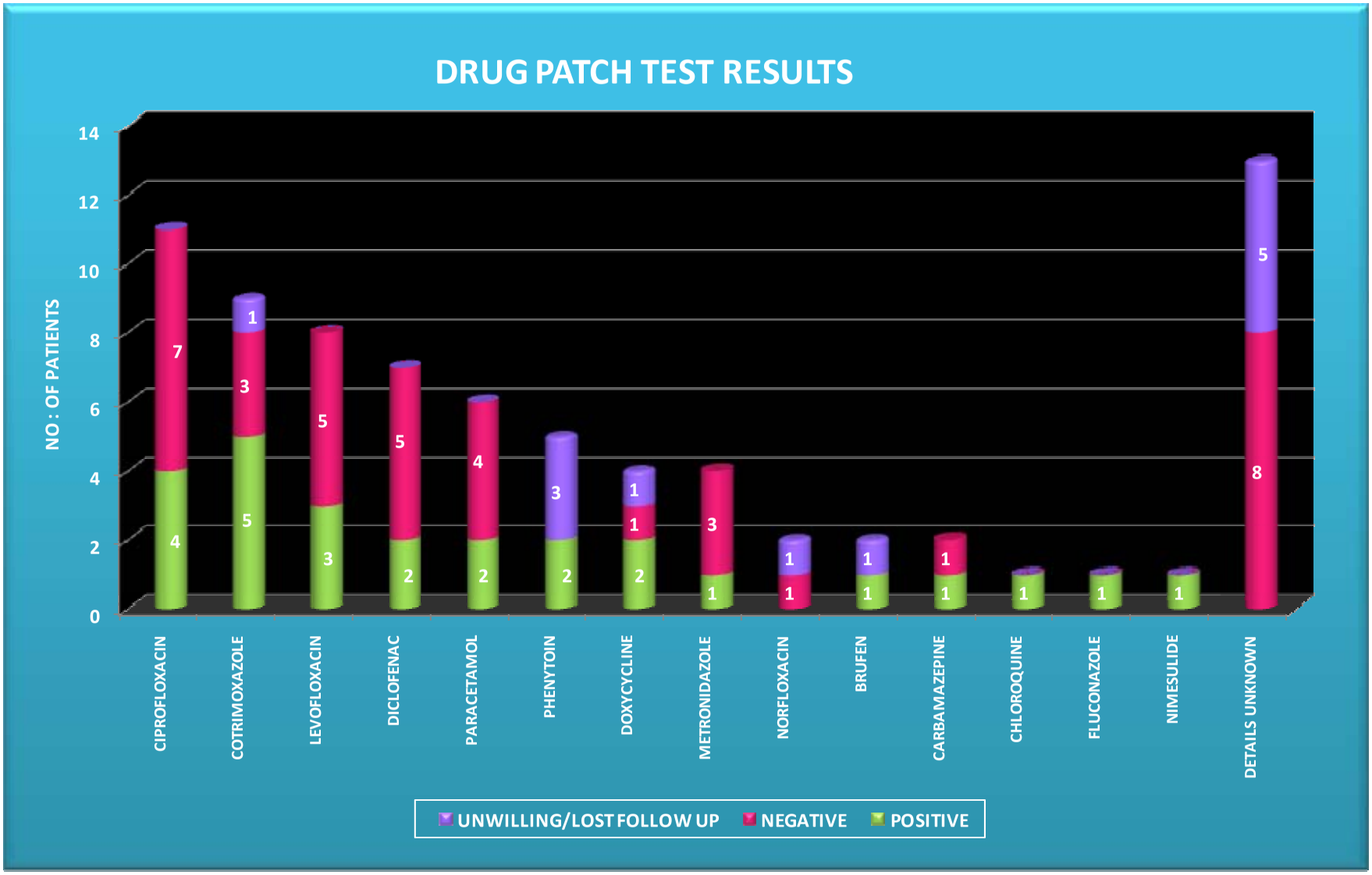
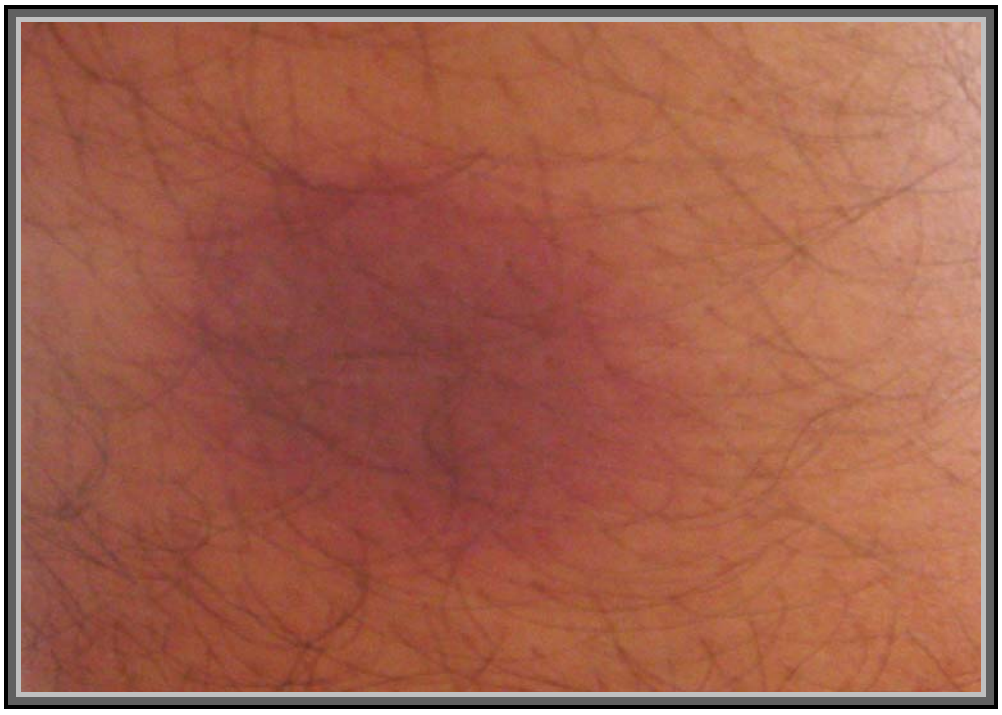
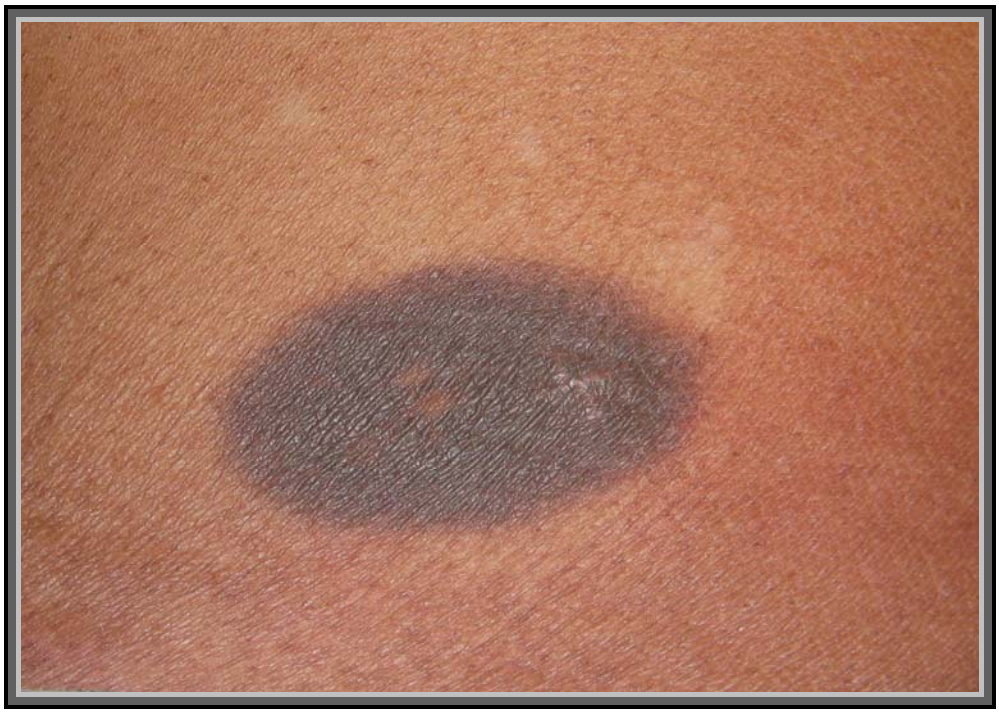

DRUG PATCH TEST RESULTS
NO : OF PATIENTS
0
2
4
6
8
10
12
14
CIPROFLOXACIN
COTRIMOXAZOLE
LEVOFLOXACIN
DICLOFENAC
PARACETAMOL
PHENYTOIN
DOXYCYCLINE
METRONIDAZOLE
NORFLOXACIN
BRUFEN
CARBAMAZEPINE
CHLOROQUINE
FLUCONAZOLE
NIMESULIDE
DETAILS UNKNOWN
UNWILLING/LOST FOLLOW UP
NEGATIVE
POSITIVE

Figure 7

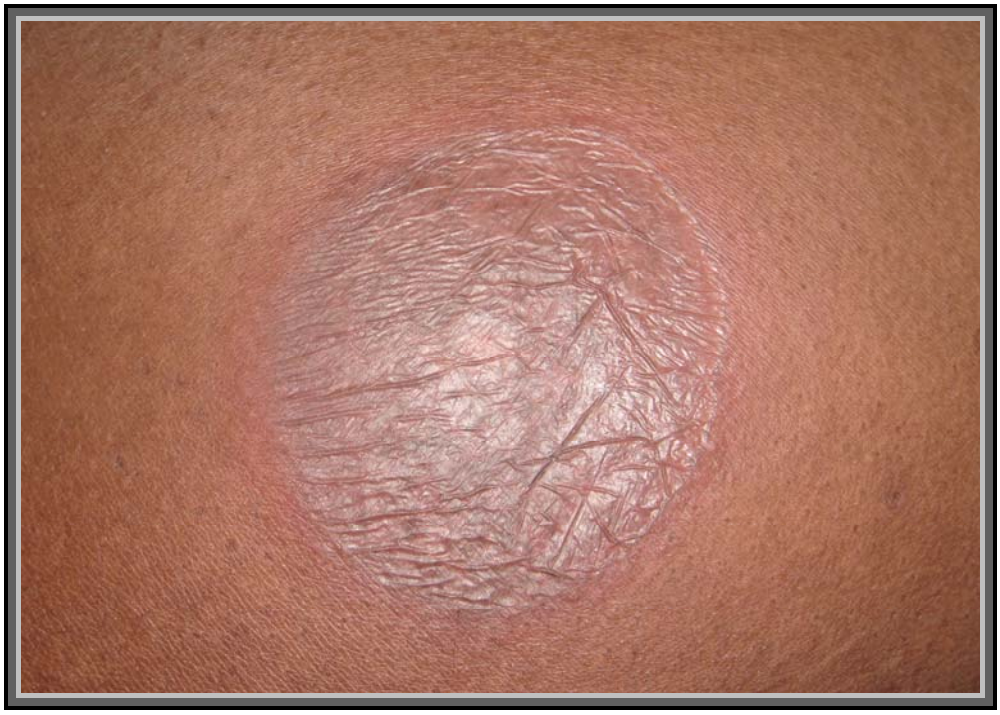
FDE - ACUTE LESION (ERYTHEMATOUS PATCH)



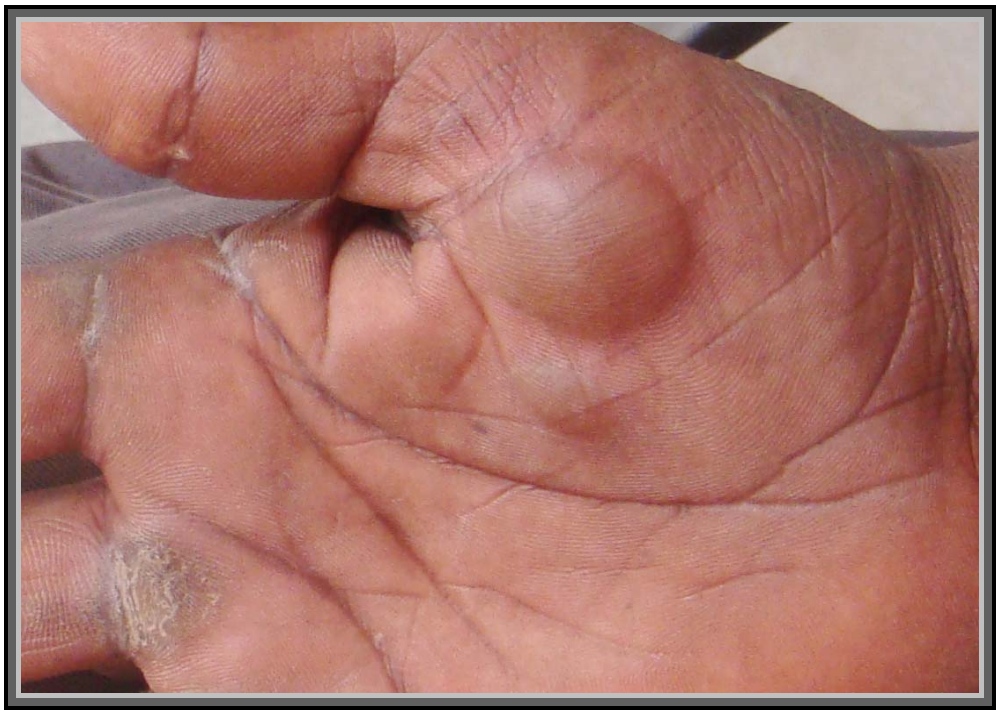
FDE - CHRONIC RESIDUAL HYPERPIGMENTED PATCH



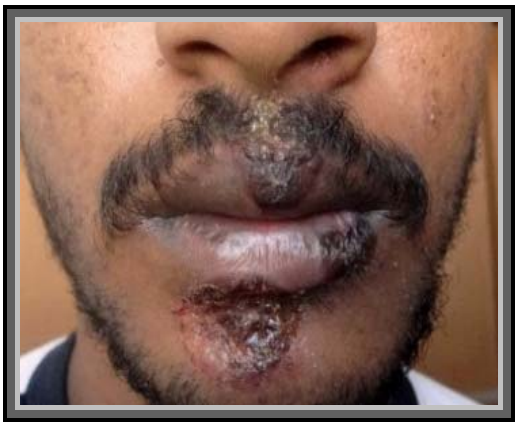
BULLOUS FDE : EARLY LESION



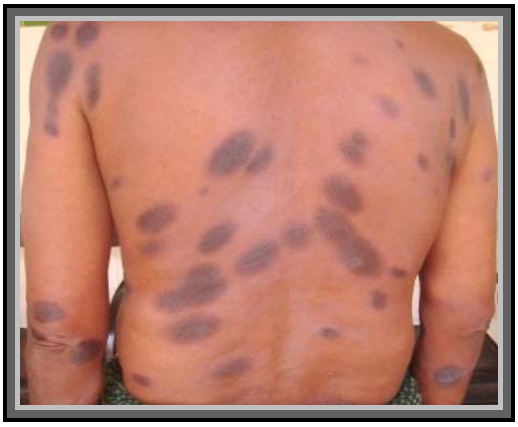
BULLOUS FDE : FULLY DEVELOPED LESION



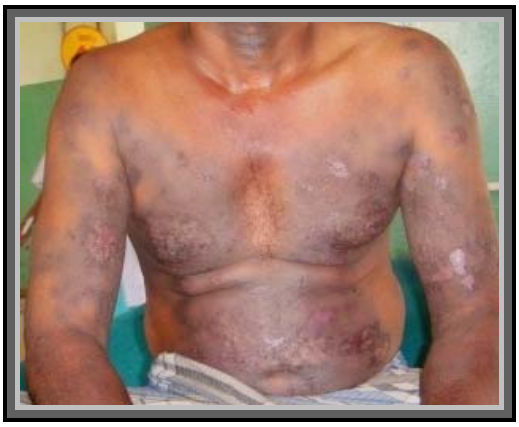
FDE - SITE OF INVOLVEMENT



FDE Involving Lips and Perioral Area

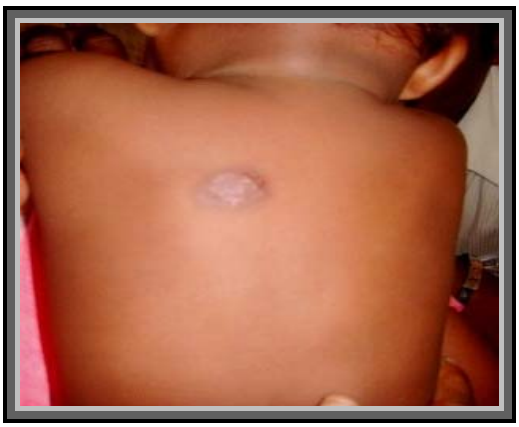


Multifocal FDE involving trunk and Upper Limb



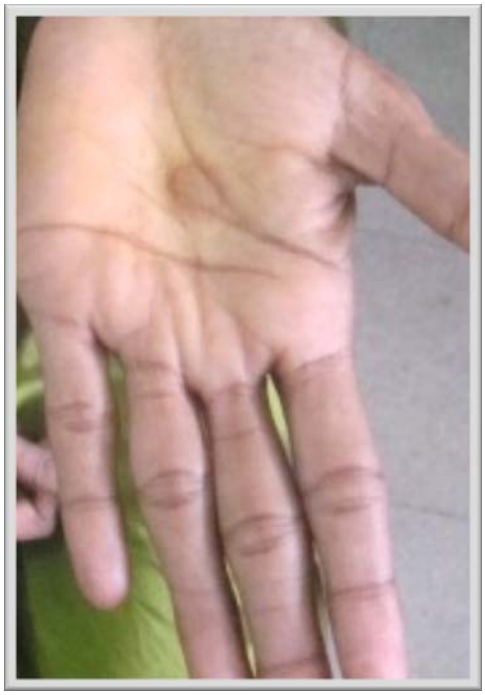
Generalised FDE - lesions on trunk and upper limbs

FDE involving extremities

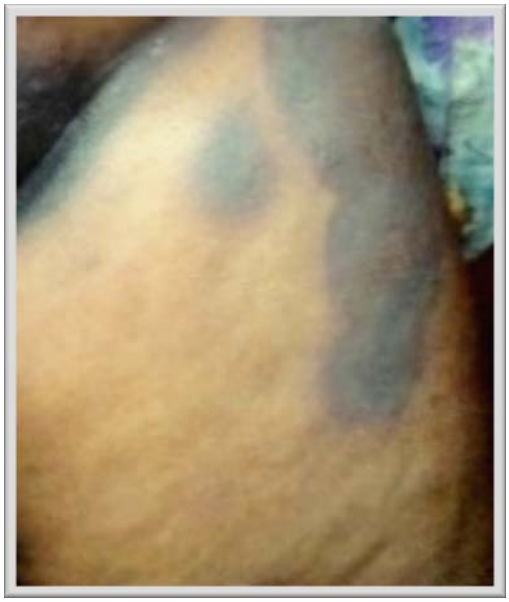


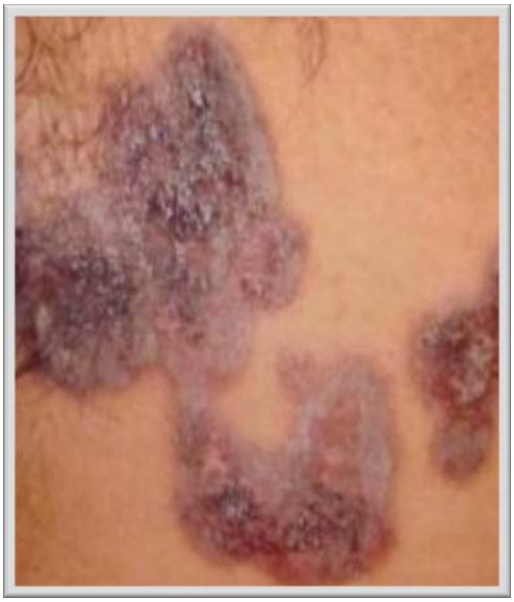
Solitary FDE in a 8 months old infant involving trunk

FDE ON THE LEFT PALM



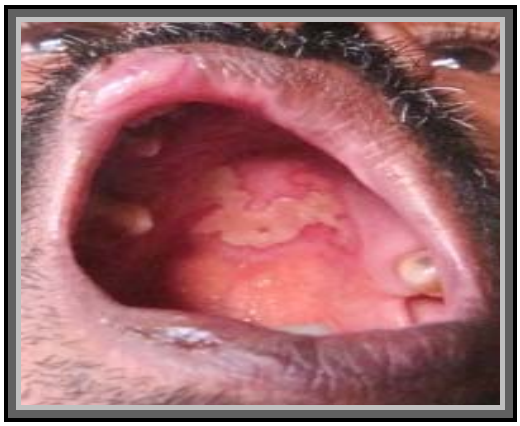
POLYCYCLIC FIXED DRUG ERUPTION





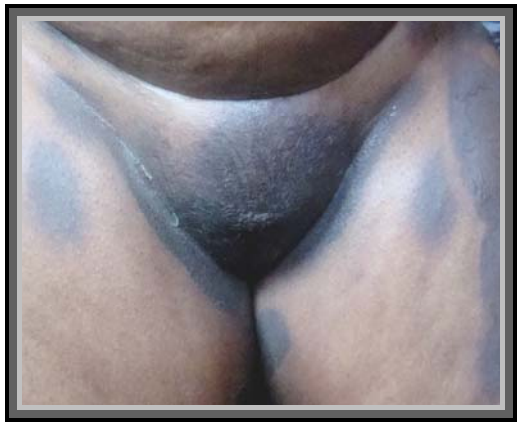
MUCOSAL FDE

FDE Involving Upper Lip and Labial Mucosa



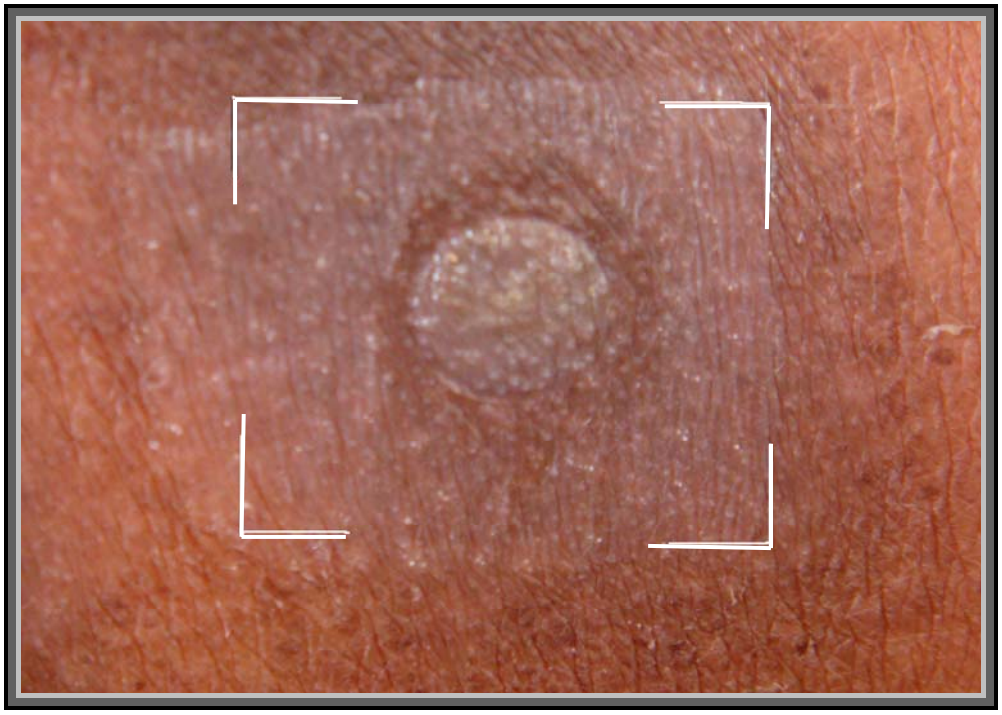
FDE Involving Upper Lip and Hard Palate

FDE involving the glans penis

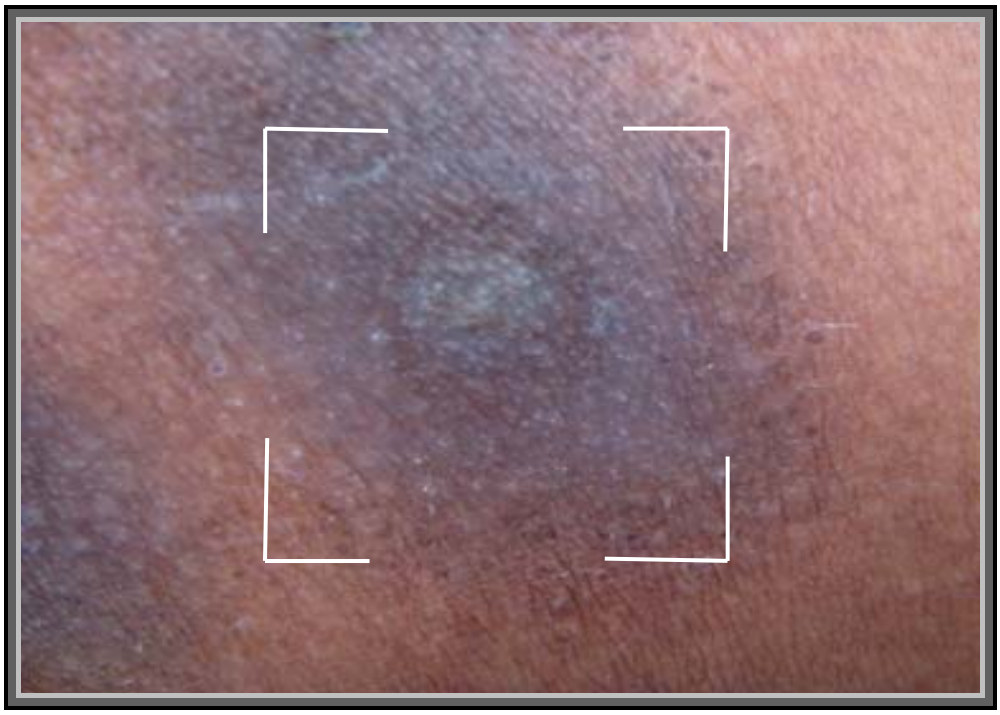


Multifocal FDE with Vulval Lesions

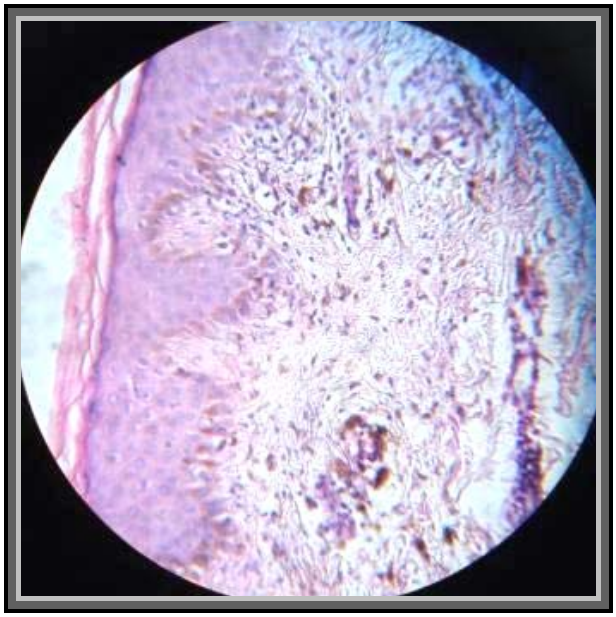
PATCH TEST - POSITIVE FOR CIPROFLOXACIN



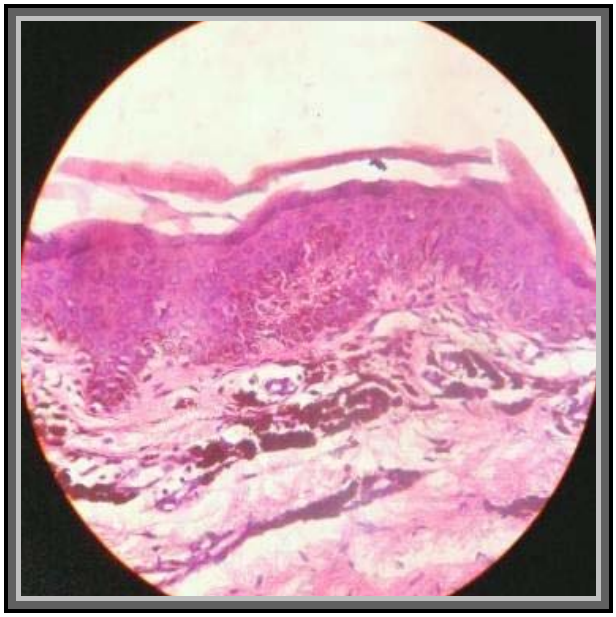
PATCH TEST - POSITIVE FOR DOXYCYCLINE



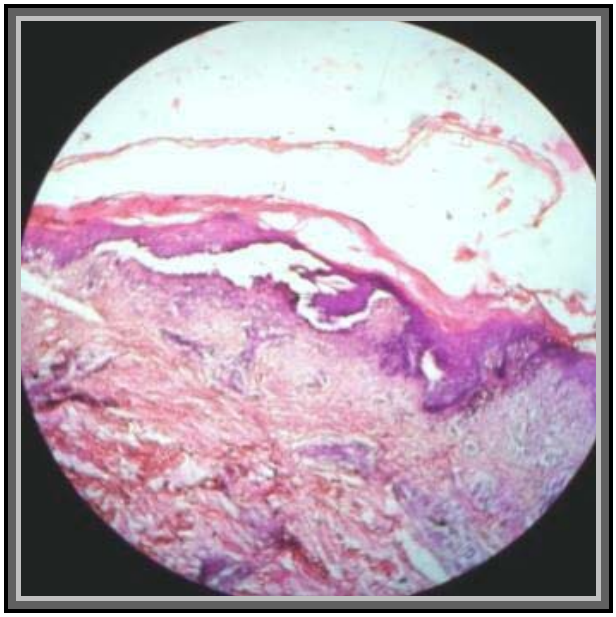
HISTOPATHOLOGY OF FDE



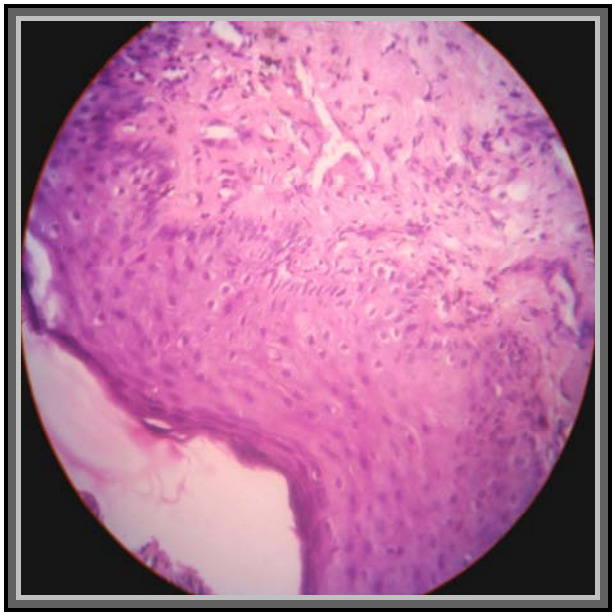
H & E section of acute FDE showing moderate acanthosis, basal cell degeneration, necrotic keratinocytes, pigment incontinence and dilated vessels



H & E section of chronic FDE showing foci of basal cell degeneration and dense melanophages in the upper dermis

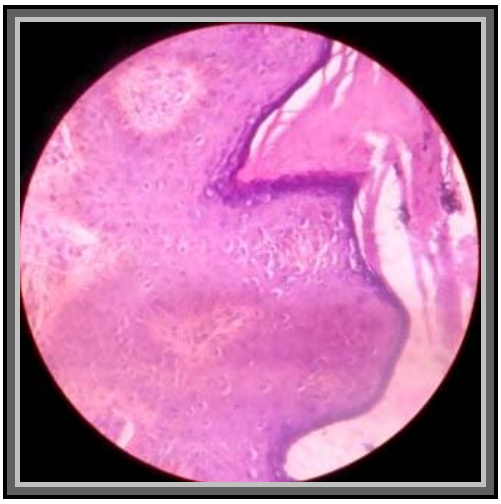


H & E Section of BULLOUS FDE - Subepidermal bulla with inflammatory infiltrates in the upper dermis

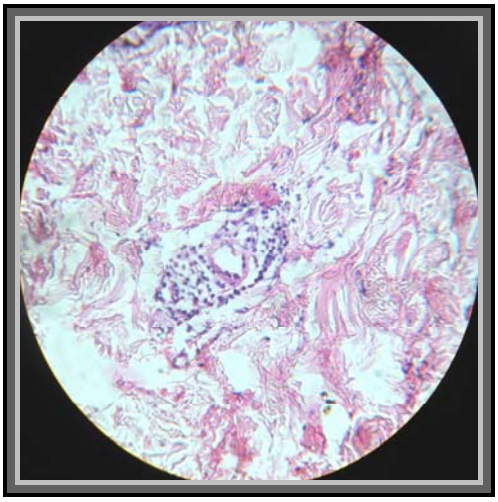


HPE OFGENITAL FDE (40x view) with Irregular acanthosis, mild spongiosis, basal cell degeneration, necrotic keratinocytes subepidermal infiltrates and dilated dermal blood vessels

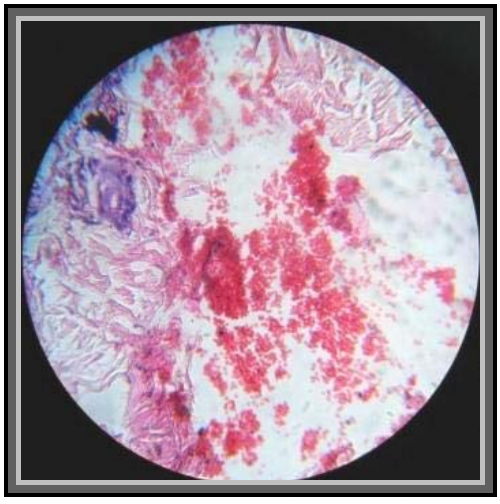
HISTOPATHOLOGY OF FDE



H & E section (40x view)
dyskeratotic cells

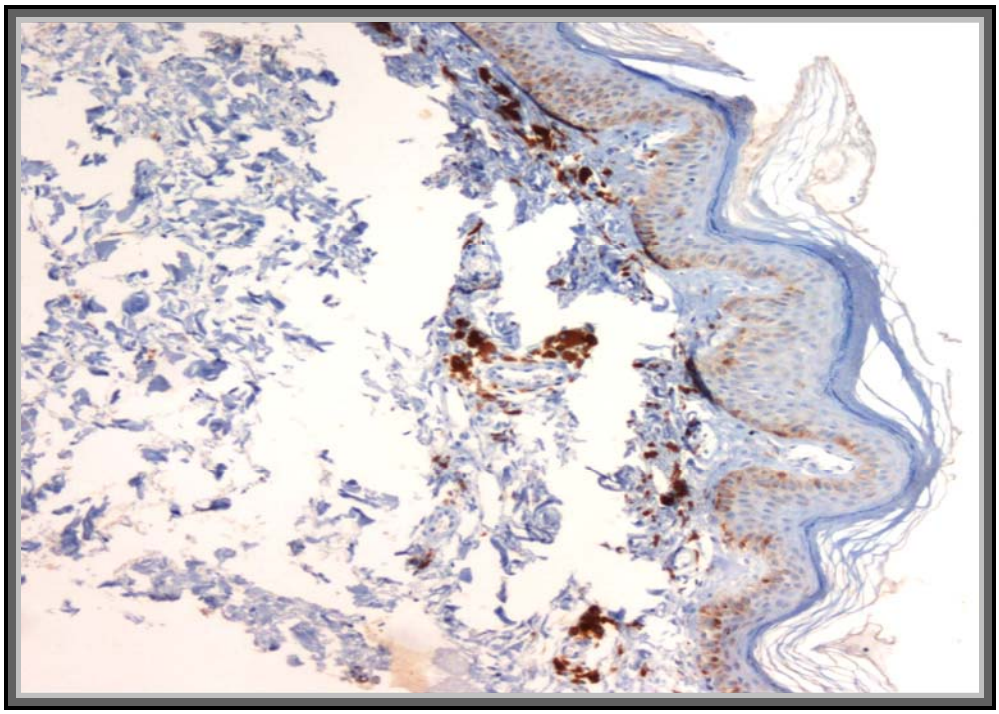


H & E section (40x view)
perivascular infiltrate

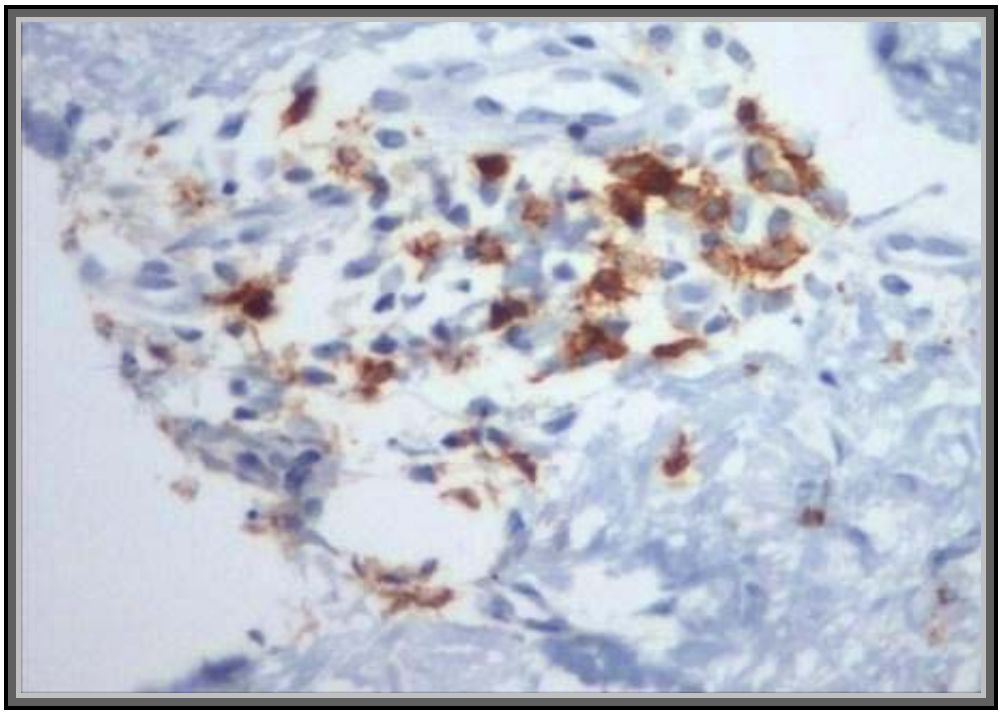


H & E section (40x view)
extravasated RBCs

IMMUNOHISTOCHEMISTRY OF FDE (ACUTE LESION)

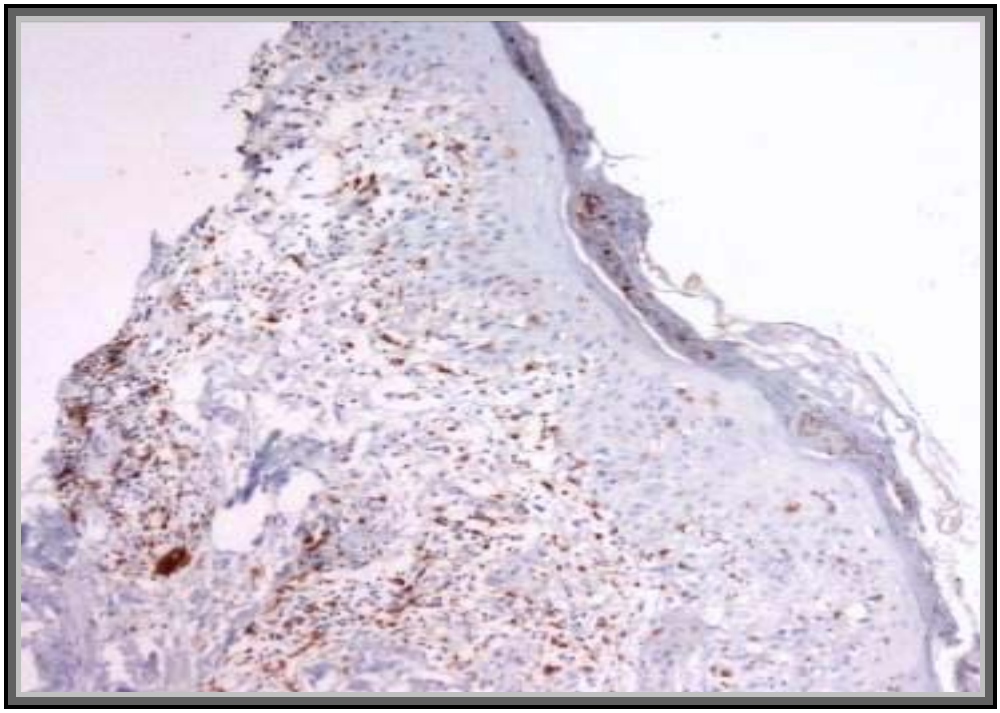


IHC(10x view) of acute FDE lesion showing intraepidermal CD8+ T-cells in the basal layer and dense collection of CD8+ T-cells in the upper dermis.

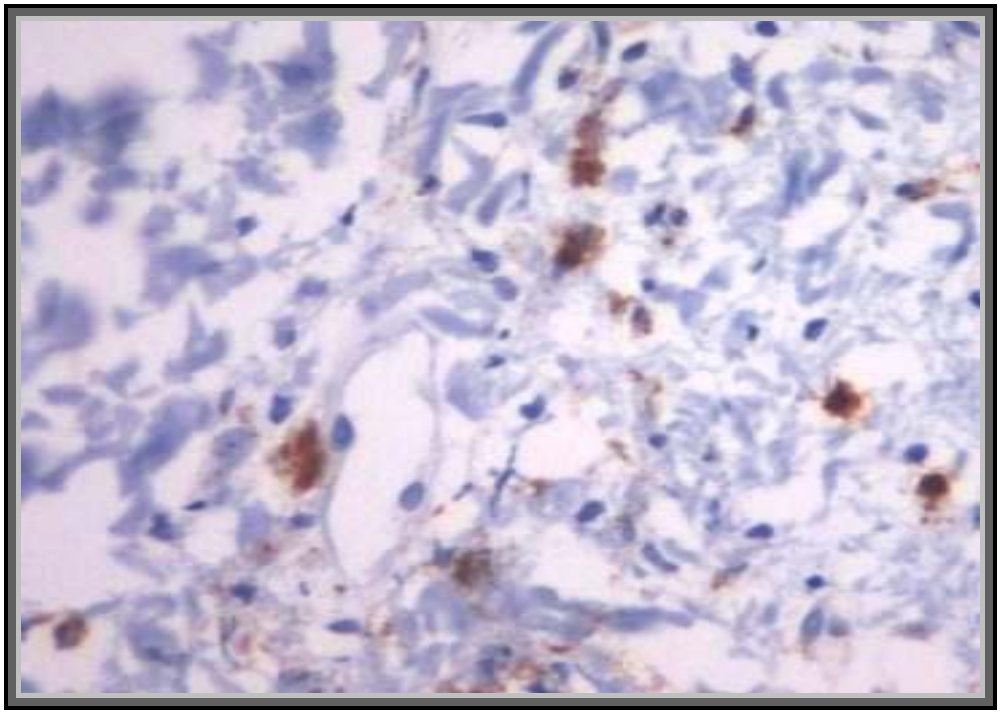


IHC (40x view) of acute FDE lesion showing dense collection of CD8 + T-cells in the upper dermis

IMMUNOHISTOCHEMISTRY OF FDE (CHRONIC LESION)



IHC (10x view) of chronic lesion showing diffuse sparse collection of CD8+T-cells in the upper dermis



IHC (40x view) of chronic FDE lesion showing sparse CD8+T-cells